CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203565Orig1s000

MEDICAL REVIEW(S)

M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: July 21, 2013

From: Kathy M. Robie-Suh, M.D., Ph.D.
Medical Team Leader, Hematology
Division of Hematology Products
Office of Hematology and Oncology Products, CDER

Subject: Medical Team Leader Secondary Clinical Review
NDA 203565, submitted 1/30/2013 (received 1/30/2013); updated clinical safety information, submitted 3/13/2013 and 3/20/2013 (received 3/13/2013 and 3/20/2013)
Injectafer (VIT-45, ferric carboxymaltose injection; FCM) for the treatment of iron deficiency anemia
Sponsor: Luitpold Pharmaceuticals, Inc.

To: NDA 203565

This application seeks approval of Injectafer (ferric carboxymaltose) for the broad indication of the treatment of iron deficiency anemia. The proposed dosing is 15 mg/kg up to a maximum single dose of 750 mg of iron on two occasions separated by at least 7 days up to a cumulative dose of 1500 mg of iron delivered by intravenous infusion or injection.

Background:
This is a resubmission for this application which was initially submitted on September 30, 2011. Clinical review of the original submission found the application acceptable for approval from a clinical viewpoint (M. Lu, 6/8/2012; K. Robie Suh, 7/20/2012). However, the application was not able to be approved due to Chemistry, Manufacturing and Controls (CMC) deficiency for the drug product manufacture leading to an overall withhold recommendation for the inspections of the manufacturing and testing facilities (see CDTL review, 7/21/2012). A Complete Response (CR) letter for the application was issued on July 23, 2012.

The current resubmission is intended to address all the CMC concerns in the July 23, 2012 CR letter. In addition on March 13, 2013 and March 20, 2013 the sponsor provided updated safety information for the drug (Periodic Safety Update Report (PSUR) from Luitpold covering June 18, 2011-June 17, 2012 and PSUR Addendum from Vifor Pharma covering June 18, 2012-January 31, 2013). The initial clinical review (M. Lu, 6/8/12) included safety data up to June 17, 2011. The primary clinical review of this resubmission and Safety Updates has been conducted by M. Lu, (signed 7/9/2013).

Ferric carboxymaltose (brand name Ferinject^{R}) is currently approved in the European Union and a number of other countries (first approval 7/6/2007 in The Netherlands), mainly for the

indication stated as "for treatment of iron deficiency when oral iron preparations are ineffective or cannot be used. The diagnosis must be based on laboratory tests." Generally the product is labeled that use is contraindicated in cases of known hypersensitivity to Ferinject or to any of its excipients, in anemia not attributed to iron deficiency, and where there is evidence of iron overload or disturbances in utilization of iron. In some countries it is also contraindicated in pregnant women in the first trimester.

Safety Update:
June 18, 2011 through June 17, 2012 PSUR (3/13/2013 submission): From June 18, 2011 through June 17, 2012 the sponsor reports 1,004 patients randomized to Ferinject and 485 patients exposed to Ferinject in clinical trials. Postmarketing exposure was estimated to be 197,291 patient years during this time with estimated total of 482,868 patient years of exposure. The sponsor reports in total 700 new cases of adverse events. Of these cases 149 patients experienced serious events of which 53 were unlisted.
There were 9 deaths reported during this time all due to serious unlisted adverse events. Two cases (both postmarketing) were considered related to Ferinject. These were:

- A 56 year old woman with "asiderotic anaemia"who received 100 mg of Ferinject over 15 minutes and began to experience dyspnea, agitation, bronchospasm and cardiorespiratory arrest beginning 5 minutes after start of the infusion. The infusion was stopped and patient received adrenaline, ketamine and other interventions but suffered neurological damage due to severe ischemia and she expired several days later. Event was considered related to Ferinject. The patient had also received pneumococcal vaccination 15 minutes prior to start of event which sponsor states as alternative explanation for the event.
- An 80 year old woman with multiple medical problems including global heart failure, chronic heart disease, hypertension and hyperthyroidism received 500 mg of Ferinject diluted in 250 mL administered over 30 minutes for iron deficiency anemia. She presented 6 hrs later with left hemiparesis and was confirmed as having a partial middle cerebral artery stroke. She died approximately (b) (6) later. Event was considered possibly related to Ferinject.

The other fatal events (not considered drug-related) were: myocardial infarction (3 patients); increasing respiratory insufficiency in 1 patient with lung neoplasm; severe respiratory tract infection and cardiorespiratory arrest in 1 patient; 1 patient due to cardiac failure (b) (6) after receiving Ferinject; 1 patient due to cardiac failure, pulmonary edema, and renal failure (b) (6) (b) (6) after receiving Ferinject.

The sponsor indicates that cumulatively through December 31, 2011 there have been 236 hypersensitivity associated cases of which 178 were serious (sponsor calculated rate of 0.045% for serious hypersensitivity cases). The events were reported as occurring within 30 minutes post dose in 56.4% (133/236) of cases; however, in 21.6% of cases timing of the hypersensitivity reaction was not reported. The sponsor states no patients died due to hypersensitivity reactions. Hypersensitivity events occurred at single doses ranging from 50-1,500 mg iron in most cases (155/236). From June 18, 2011 through June 17, 2012 there were 13 new reports of hypersensitivity reactions, 8 serious. The sponsor indicates there were no reported deaths due to hypersensitivity. Outcome was not reported for 3 cases.

June 18, 2012 through January 31, 2013 PSUR Bridging Report (3/20/2013 submission):
From June 18, 2012 through January 31, 2013 the sponsor reports an additional 194,300 patient years of exposure to give an estimated total cumulative postmarketing exposure through January 31, 2013 of 677,168 patient years. During this time also an additional 326 patients were enrolled in clinical trials (163 receiving Ferinject [53 pregnant women, 17 patients with chronic heart failure and an additional estimated 93 (blinded) patients with chronic heart failure]). The sponsor reports a total 544 new cases of adverse events (108 serious)(excludes 17 cases [4 serious] from consumers). There were 47 serious unlisted cases. There were 7 fatal cases, including 2 fetal deaths. Only one fatal case was deemed related to Ferinject: a 58 year old woman with pulmonary non-Hodgkin's lymphoma, post-actinic cardiomyopathy, and other illnesses who experienced Grade IV hypersensitivity reaction and anaphylactic shock with dyspnea, hypotension, and bradycardia beginning 3 minutes after start of Ferinject infusion (received about 36 mg iron in 30 mL saline) and died.

Pregnancy-related cases of serious unlisted events including fetal deaths are described in Dr. Min Lu's Medical Officer Review (July 9, 2013). There were 7 pregnancy-related serious unlisted event cases and 6 fetal deaths. One patient died as described above and one recovered with unspecified sequelae. There were 18 cases of hypersensitivity that had some unlisted event term among the listed events. These are shown in the table below.

Table 3 Unlisted Events per Case Deemed as a Hypersensitivity Case

Case Number	Unlisted HSR Event
VIT-2012-02347[1]	Circulatory problems and cyanosis
VIT-2012-02507[1]	Cardiac arrhythmia
VIT-2012-02992	Allergic rhinitis and conjunctivitis
VIT-2012-03006	Papules
VIT-2012-03179[1]	Collapse vascular
VIT-2012-03565	Fatal outcome (see Section 6.5)
VIT-2012-03680[1]	Polyuria
VIT-2012-03681	Oxygen saturation decreased
VIT-2012-03693[1]	Throat tingling and throat discomfort
VIT-2012-03702[1]	Collapse
VIT-2012-03709[1]	Circulatory collapse
VIT-2012-03718[1]	Respiratory depression
VIT-2012-03820	Anaphylactic shock[2] and respiratory distress
VIT-2012-03980	Foetal bradycardia (see Section 6.6)
VIT-2012-04014[1]	Cyanosis
VIT-2012-04072	Increased blood pressure, cyanosis and face-oedema
VIT-2012-04331	Red plaques on thighs and little petechial area on left groin and right knee
VIT-2013-00023	Asthma attack

1 HSR was not a reported diagnosis, these cases were assessed as HSR by the MAH.
2 As no antibodies specific to Ferinject have been detected, the MAH codes the anaphylactic reaction as anaphylactoid reaction, which is a listed event.
Notes: HSR = Hypersensitivity; MAH = Marketing authorisation Holder.

No increases in frequency of certain identified events, including hypersensitivity, hemosiderosis, cardiotoxicity, hyperphosphatemia, overdose or hypertension were identified.

The data in the safety updates did not raise new safety concerns or change the overall benefit-risk assessment. Post-marketing data should be reflected in the labeling.

Sponsor's proposal to address Pediatric Research Equity Act (PREA):
No pediatric patients were studied for the current NDA. To address PREA (Pediatric Research Equity Act) the sponsor requests a waiver for patients less than (b)(4) years of age and requests a deferral for studies in pediatric patients (b)(4) to 17 years of age.

Waiver Request (ages birth to less than (b)(4) years):
The sponsor has requested a waiver for pediatric patients birth to (b)(4) years. Regarding this age group the sponsor states:

> "Based on our previous pediatric experience with our other approved IV iron (Venofer), recruiting patients from birth to (b)(4) years of age into our Phase III trials (Post marketing study) was waived by the Division.
>
> Luitpold Pharmaceuticals, Inc., respectfully requests a waiver from conducting a pediatric study in the 0-(b)(4) years of age group due to logistical challenges associated with subjects of this age range. This request for a waiver is to meet the requirements of Pediatric Research Equity Act (PREA)."

It should be noted that pediatric studies of Venofer for iron deficiency anemia in patients age <2 years with non-dialysis dependent chronic kidney disease (CKD) receiving or not receiving an erythropoietin were waived (NDA 21-135 letter dated June 17, 2005) (too few children with disease to study). With the original approval of Venofer for iron deficiency anemia in patients with hemodialysis-dependent chronic kidney disease, pediatric studies of Venofer in neonates and infants were not required, however, a post-marketing commitment (PMC) #1 requested additional information for possible need for and risks involved with Venofer® use in very young pediatric patients (approval letter dated November 6, 2000). A letter was sent to the sponsor on December 6, 2001 that PMC #1 for Venofer had been fulfilled.

Deferral Request (ages (b)(4) years to 17 years):
For pediatric patients age (b)(4) to 17 years the sponsor proposes to conduct two trials of Injectafer: (1)a pharmacokinetic/pharmacodynamic (PK/PD) study to characterize the PK of serum iron and determine appropriate dosing of FCM for the pediatric population with iron deficiency anemia and (2)a safety and efficacy trial of FCM versus iron sucrose.

I concur with Dr. Lu's recommendation in the previous Clincal Review (signed 6/8/2012) that pediatric studies in this age range may be deferred.

Following is suggested wording for the post-marketing requirements (PMR) to address PREA:

1. Identify an optimal dose of Injectafer for the pediatric patient population. Conduct one or more pharmacokinetic (PK) and pharmacodynamic (PD) trials in pediatric patients aged (b)(4) to < 17 years with iron deficiency anemia sufficient to justify and to

characterize the dose to be tested in a confirmatory clinical trial of safety and efficacy. Identify the most relevant PD endpoints to measure.

2. Determine the safety and efficacy of ferric carboxymaltose in pediatric patients aged (b) (4) to <17 years with iron deficiency anemia by conducting a randomized, active-controlled clinical trial. (b) (4)

Conclusions and Recommendations:
The sponsor has provided updated safety information in this submission. Overall, from a clinical perspective the benefit-risk assessment for approval of ferric carboxymaltose injection (Injectafer) with dosing of 15 mg/kg up to a maximum single dose of 750 mg of iron on two occasions separated by at least 7 days up to a cumulative dose of 1500 mg of iron delivered by intravenous infusion or injection remains favorable for the treatment of iron deficiency anemia in patients who are intolerant or had unsatisfactory response to oral iron and in patients with non-dialysis dependent chronic kidney disease.

Labeling:
Recommendations for the labeling were included in the CR letter sent to the sponsor on July 23, 2012. However, it appears that by and large Agency recommendations from that draft labeling were not incorporated in the sponsor's labeling included in the resubmission.

Recommendations for labeling are as provided in the previous clinical reviews (M. Lu, 6/8/2012; KM Robie Suh, 7/20/2012) and Dr. Lu's 7/9/2013 review.

Importantly, it should be noted that in the draft labeling sent to the sponsor with the Complete Response letter the Agency recommended wording of the indication to be approved as:

(b) (4)

Thus, the sponsor seeks to include patients with iron deficiency anemia [redacted] without further specification as a labeled population in the Indications section of the label. In Study 1VIT0903 in Cohort 2 the sponsor allowed enrollment of "Subjects whose physicians feel the subject is inappropriate for a 14 day course of oral iron (e.g., baseline Hgb is sufficiently low that the patient requires rapid repletion of iron stores to minimize the risk of eventually needing a blood transfusion [e.g., Hgb <8 g/dL unless there is evidence of cardiac or respiratory dysfunction in which case IV iron may be used without oral run-in if Hgb <9 g/dL]) but who otherwise satisfy the entry criteria". This population of patients (who did not participate in the 14 day oral iron run-in in this study) constituted 337 (33.8%) of the 997 patients enrolled in the study. The mean baseline hemoglobin in Cohort 2 was 9.1 g/dL (median, 9.1 g/dL) as compared to a mean of 10.6 g/dL (median, 10.7 g/dL) among patients in Cohort 1 (who were able to complete the oral iron run-in period). For most of these 337 patients the reason given for inclusion in Cohort 2 without oral iron run-in was given as "low hemoglobin". About 130 patients in Cohort 2 had "Other" reasons listed for not undergoing run-in. The main "Other" reason given was some history of oral iron intolerance (about 77 patients), followed by history of unresponsiveness to oral iron in a smaller number (about 15 patients). Several patients had history of gastric bypass or other gastrointestinal surgery; several had malabsorption due to other gastrointestinal disorders. Thus, it appears that the majority of these "Other" patients who were enrolled in Cohort 2 without first entering the oral iron run-in period had intolerance or unresponsiveness to oral iron based on medical history. About 74% of patients in Cohort 2 were listed as having previous iron therapy.

In conclusion, it seems reasonable to conclude that the great majority of patients enrolled in Study 1VIT09031 had some exposure or trial of oral iron at some time prior to being randomized in the study and were considered for parenteral iron due to intolerance or inadequate response. The small group of patients with various gastrointestinal disorders and other reasons for receiving parenteral iron in the study (<5% of patients) is not sufficient to support a specific claim in the indications statement in the label.

Finally, only patients with non-dialysis dependent chronic kidney disease (CKD) were enrolled in the CKD study (1VIT09030) submitted to support this application. Therefore, the labeled CKD population should be limited to patients with non-dialysis dependent chronic kidney disease.

Post-marketing Studies:
With regard to clinical post-marketing studies, a waiver for pediatric studies required under PREA for the indication should be granted for studies of Injectafer in patients less than [redacted] years of age, because of too few children with the disease to study. A post-marketing requirement to study Injectafer in pediatric patients [redacted] years to <17 years should be included with the approval. A deferral for these studies should be granted to allow time for the final protocols to be developed and the studies to be conducted. Protocols for proposed studies should be submitted for review.

Reviews and recommendations from other disciplines should be considered for decision on regulatory action, labeling and post-marketing commitments.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATHY M ROBIE SUH
07/22/2013

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Division Director
Subject	Division Director Summary Review
NDA/BLA # Supplement #	203565
Applicant Name	Luitpold Pharmaceuticals, Inc.
Date of Submission	10/03/11
PDUFA Goal Date	8/03/12
Proprietary Name / Established (USAN) Name	Injectafer/Ferrous Carboxymaltose
Dosage Forms / Strength	For injection
Proposed Indication(s)	For the treatment of iron deficiency anemia
Action/Recommended Action for NME:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Min Lu, M.D./Kathy Robie-Suh, M.D./Ph.D.
Statistical Review	Kyung Y. Lee, Ph.D./Mark Rothmann, Ph.D.
Pharmacology Toxicology Review	Brenda Gehrke, PhD./Haleh Saber, Ph.D.
CMC Review/OBP Review	Sue Ching Lin, Ph.D./Janice Brown, Ph.D.
Microbiology Review	John Metcalfe, Ph.D./Stephen Langille, Ph.D.
Clinical Pharmacology Review	Bahru Habtemariam, Ph.D./Julie Bullock, Pharm.D.
DDMAC	James Dvorsky
DSI	David X. Gan, M.D./Leslie Ball, M.D. Anthony Orencia, M.D./Janice K. Pohlman, M.D./Susan D. Thompson, M.D.
CDTL Reviews	Kathy Robie-Suh, M.D., Ph.D.
OSE/DMEPA	
OSE/Epidemiology	
OSE/DRISK	
Other - statistical safety	
Other – Maternal Health Team Other-	Karen Feibus, M.D./ Lisa Mathis, M.D.

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology

Signatory Authority Review Template

1. Introduction

Luitpold submitted this application as a complete response to a non-approval letter received for ferrous carboxymaltose (FCM).

An application for ferrous carboxymaltose was originally submitted on July 5, 2006 as NDA 022054 and received a non-approval letter on July 9, 2007 due to clinical safety concerns. Since that time the applicant has resubmitted the application on September 18, 2007 and received another non-approval letter on March 11, 2008 due to clinical safety concerns.

The applicant responded to the March 11, 2008 complete response letter on October 3, 2011.

The PDUFA goal date is August 3, 2012.

From Dr. Lu's review:

FCM has been authorized for use and marketed in other countries by Vifor Pharma or a subsidiary company since 2007. It is currently registered under 3 different trade names: Ferinject®, Injectafer®, and Iroprem®, varying by country. As of 17 June 2011, the product is approved for use and marketed in 20 European countries. It has been approved but it has not yet been marketed in 15 other countries. The Summary of Product Characteristics in U.K. lists that Ferinject is indicated for treatment of iron deficiency when oral iron preparations are ineffective or cannot be used.

2. Background

Products to treat iron deficiency include oral as well as injectable preparations. The iron injection products are available by prescription only. The oral iron products are available without a prescription.

The currently marketed products are:

Iron dextran (InFed and generics): indicated for patients with iron deficiency (any cause) who are assessed as not appropriate for oral iron therapy.
Ferrlecit (ferric gluconate): indicated for patients with iron deficiency who are undergoing dialysis and receiving erythropoietin therapy.
Venofer (iron sucrose): indicated for patients with iron deficiency who are:
-non-dialysis chronic kidney disease patients (either receiving an erythropoietin or not)
-hemodilaysis patients receiving an erythropoietin
-peritoneal dialysis patients receiving an erythropoietin

Luitpold originally submitted an application to market Ferrous Carboxymaltose (proposed tradename – Ferinject) in 2006 for the following indications:

is an intravenous iron product indicated for the treatment of iron deficiency anemia in:
- *Heavy Uterine Bleeding*
- *Postpartum*
- *Inflammatory Bowel Disease and*
- *Hemodialysis patients*

The application received a non-approval letter due to safety concerns. Review of the controlled studies for the indication showed an imbalance in deaths observed in controlled trials. More deaths occurred in the ferrous carboxymaltose treatment arms than in the control subjects.

The original database had 8 randomized controlled trials in subjects who were post-partum, had uterine bleeding, had inflammatory bowel disease, or were receiving hemodialysis. The control treatment was oral iron for the all trials with the exception of the hemodialysis trial.

Dr. Rieves's summary review noted:

Overall, the totality of the efficacy data supports the Ferinject dose regimen's efficacy in a pattern indicative of acceptable treatment of iron deficiency anemia, regardless of the cause for the iron deficiency…

Overall, the most notable safety findings relate to:
-mortality among subjects receiving Ferinject

-increased rate of serious adverse events among subjects receiving Ferinject, compared to oral iron
-clinically important hypophosphatemia

Dr. Rieves also noted that no clinical data was provided to support the safety of repeated "cycles" of ferrous caboxymaltose injections.

Luitpold received a non-approval letter requesting that any resubmission provide the following:

Clinical data to resolve the safety risks identified (excess mortality and severe hypophosphatemia) and verify the safety of more than one iron replenishment cycle

The following text from Dr. Lu's review highlights Agency and Applicant interactions from the receipt of the Complete Response letter.

The Agency issued a Not Approvable action on March 11, 2008. The letter indicated that the risk for mortality must be more thoroughly assessed and additional safety data should be obtained from clinical studies of Injectafer use among the applicable patient population of women who are intolerant to oral iron or who had an unsatisfactory response to oral iron. The Agency recommended that these studies use appropriate control groups in order to meaningfully interpret the data. The Agency stated that the proposed dosage regimen may deliver an excessive iron dose during a single administration and recommended that the sponsor consider the development of an alternate dosage regimen that delivers a lower (single dose) amount of iron. A meeting was held on May 18, 2009 under IND 63,243 between the Agency and the sponsor to discuss the proposed further clinical studies (1VIT09031 and 1VIT09030) to evaluate the efficacy and safety of a low dose of Injectafer (maximum single dose of 750 mg with maximum total dose of 1500 mg) in patients who are intolerant to oral iron or who had an unsatisfactory response to oral iron with a oral iron run-in period and also in patients with chronic renal disease (CKD). The Agency agreed on the proposed studies and the proposed cardiovascular composite safety endpoint to be evaluated in these studies. In the proposed studies, other intravenous iron were selected as control in patients with CKD and in patients who are intolerant to oral iron. The Agency emphasized the double-blind design to assess the safety endpoint.

3. CMC/Device

Drs. Lin and Pope-Miksinski and Ms. Brown reviewed this applicaiton. In their reviews they state the following:

From the perspective of chemistry, manufacturing, and controls, this NDA may be approved, pending an "acceptable" overall recommendation from the Office of Compliance for the inspections of the manufacturing and testing facilities for the drug substance and drug product.

Based on the provided stability data, a 24-month expiration dating period is granted for the drug product when stored at the proposed controlled room temperature.

However, the Office of Compliance has issued a Withhold recommendation; therefore the Injectafer application cannot be approved. The initial decision was made in February 2012 and revisted in July 2012 and the recommendation stands.

4. Nonclinical Pharmacology/Toxicology

The pharmacology and toxicology information was referenced the previous submission under NDA 22-054. This application was reviewed and no deficiencies were identified for NDA 22-054.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology information was referenced the previous submission under NDA 22-054. This application was reviewed and no deficiencies precluding approval were identified for NDA 22-054.

6. Clinical Microbiology

The Product Quality Microbiology review recommends approval.

7. Clinical/Statistical-Efficacy

I have read NDA 22-054 summary and clinical reviews by Drs. Rieves, Robie-Suh, and Lu.

The following text is from Dr. Lu's review of this submission:

Two randomized controlled pivotal trials (1VIT09031 and 1VIT09030) were conducted to support the efficacy of Injectafer with the proposed dose regimen of 15 mg/kg with the maximum individual dose of 750 mg and a total dose of 1,500 mg. Study 1VIT09031 was conducted in patients with iron deficiency anemia who had an inadequate response to oral iron treatment, who were intolerant to oral iron during the 14-day run-in period, or who were deemed unsuitable by the Investigator for the oral iron, mainly due to low hemoglobin level with or without co-morbidities. Study 1VIT09030 was conducted in patients with non-dialysis dependent chronic kidney disease (NDD-CKD). Both clinical studies were randomized, open-label, controlled studies. In Study 1VIT09031, oral iron was used as control in patients who had an inadequate response to oral iron treatment in Cohort 1 and other IV iron products (mostly Venofer) were used as control in patients who were intolerant to oral iron in Cohort 2. In Study 1VIT09030, Venofer was used as control in patients with CKD. The primary efficacy endpoint was the mean change from baseline to the highest hemoglobin observed anytime between baseline and Day 35 or time of intervention in Study 1VIT09031 and between baseline and Day 56 or time of intervention in Study 1VIT09030.

In Study 1VIT09031, the results show that the mean increase in hemoglobin from baseline to the highest value between baseline and Day 35 or time of intervention in the Injectafer group was statistically significantly greater than that in the oral iron group in Cohort 1 (1.57 g/dL vs. 0.80 g/dL, $p<0.01$) and also higher than that in the IV standard care group (2.90 g/dL vs. 2.16 g/dL,$p<0.01$) in Cohort 2. This study demonstrated that Injectafer increased hemoglobin level in patients with iron deficiency anemia who had an inadequate response to oral iron treatment or who were intolerant to oral iron.

In Study 1VIT09031, the mean increase in hemoglobin from baseline to the highest value between baseline and Day 56 or time of intervention in the Injectafer group was

non-inferior to Venofer (1.13 g/dL vs. 0.92 g/dL, treatment difference 0.21 g/dL [95% CI 0.13-0.28 g/dL]). The results from the secondary efficacy endpoints analyses including hemoglobin response and iron indices were consistent with the primary efficacy analysis results in both studies. The results from subgroup analyses including baseline hemoglobin level and etiology of iron deficiency anemia in Study 1VIT09031 and baseline hemoglobin, EPO use and CKD stage in Study 1VIT09030 were all consistent with the results from the primary efficacy endpoint analyses. This study demonstrated that Injectafer increased hemoglobin level in patients with iron deficiency anemia in NDD-CKD population.

I concur with the conclusions of the clinical and statistical review teams regarding the demonstration of efficacy for indication.

8. Safety

During the original NDA review (22-054), the review team identified excess mortality and hypophosphatemia as areas of concern for this product.

Mortality and Cardiovascular Events
Dr. Lu's review did a focused analysis of mortality and Cardiovascular Events. The following text is from her review:

The mortality rates were similar between Injectafer for the proposed dosing regimen and the comparators in pooled analysis of the two pivotal studies (16/1775, 0.9% vs. 21/1783, 1.2%) and were also similar between Injectafer with the maximum single dose of 750 mg with the different total doses and the comparator in pooled analysis of the five clinical studies (17/2566, 0.7% vs.22/2590, 0.8%). For all completed studies, the overall mortality rate was 0.5% (33/6679) in the Injectafer-treated patients and 0.6% (30/5394) in comparator-treated patients.

In the two pivotal trials, no significant difference was found for the pre-specified primary cardiovascular composite safety endpoint (including death, MI, stroke, unstable angina, CHF, hypertension and hypotension) between Injectafer and Venofer or pooled comparators (10.8%, 11.1%, and 9.7%, respectively). Hypertensive events were found to be significantly higher in the Injectafer group as compared to the Venofer group, or the pooled comparator group (6.0%, 4.1%, and 3.5%, respectively).

Treatment-emergent serious adverse events were similar among Injectafer, Venofer, and the pooled comparators groups numerically and by organ group. The incidence of treatment-emergent serious or severe hypersensitivity/allergic adverse events was 1.5% for Injectafer and 1.6% for Venofer. Flushing and hypertension were the most common adverse events resulting in premature discontinuation from the trial.

Overall assessment of drug-related adverse events
From Dr. Lu's review:

The incidence of any drug-related treatment-emergent adverse event was greater in the FCM group (23.5%) compared with the Venofer (17.3%) and pooled comparators (15.9%) group.

The most common (≥1.0%) drug-related treatment-emergent adverse events in the FCM group were nausea (7.2%), hypertension (3.8%), flushing (2.7%), hypophosphatemia (2.1%),dizziness (2.0%), vomiting (1.7%), injection site discoloration (1.4%), headache (1.2%), ALT increased (1.1%), and dysgesusia (1.1%). Drug-related treatment-emergent adverse events that occurred more frequently (by ≥1%) with Injectafer than with pooled comparator included nausea, hypertension, flushing, hypophosphatemia, vomiting, and injection site discoloration.

I concur with the conclusions of the clinical and statistical review teams.

Dr. Lu's review recommends approval. The following is the text from her review:

From a clinical perspective, Injectafer should be approved for the indication for the treatment of iron deficiency anemia in patients who are intolerant to oral iron or have had unsatisfactory response to oral iron and in patients with non-dialysis dependent chronic kidney disease.

9. Advisory Committee Meeting

This product was discussed at a Drug Safety and Risk Management Advisory Committee Meeting on February 1, 2008. From Dr. Lu's review:

The Committee voted that the available clinical data indicated Injectafer® was associated with a mortality disadvantage compared to oral iron and recommended an unfavorable benefit-risk assessment for the proposed indication. The committee did consider the data as providing a favorable benefit-risk assessment for Injectafer in the treatment of iron deficiency anemia in post-partum women or women with heavy uterine bleeding who have had an unsatisfactory response to oral iron or were intolerant of oral iron.

10. Pediatrics

From Dr. Lu's review:

The applicant requested a deferral of pediatric studies in (b)(4) and 17 years of age group under PMRs and requested a waiver of a pediatric study in the 0-(b)(4) years of age group to meet the requirements of Pediatric Research Equity Act (PREA). The proposed pediatric studies in (b)(4) and 17 years of age group include one pharmacokinetic/pharmacodynamic study and one safety and efficacy study in

pediatric patients with iron deficiency anemia. The applicant proposed to submit full pediatric study protocols within one year of approval and recruitment will begin within the first 18 months after the NDA is approved with the final study report being submitted on or before December 31, 2016. These requests should be granted.

11. Other Relevant Regulatory Issues

The application complied with financial disclosure requirements and trials were conducted with good clinical practice.

Maternal Health Team provided labeling recommendations which were incorporated into labeling.

Office of Surveillance and Epidemiology was consulted including DMEPA who provided labeling input.

Division of Scientific Investigation (DSI)
Inspection of trial sites submitted for NDA (b) (4) did not reveal any unreliable data.
Inspection of trial sites submitted for NDA 203565 did not reveal any unreliable data.

The only unresolved regulatory issues are labeling and facilities.

12. Labeling

The labeling was reviewed by all disciplines and consultant staff. Labeling negotiations will be finalized during next cycle review.

13. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action
  Complete Response due to facility issues
- Risk Benefit Assessment
- Recommendation for Post marketing Risk Management Activities
- Recommendation for other Post marketing Study Requirements (PMR)/ Commitments (PMC)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN T FARRELL
07/21/2012

Cross-Discipline Team Leader Review

Date	July 20, 2012
From	Kathy M. Robie Suh, M.D., Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA	203565
Applicant	Luitpold Pharmaceuticals, Inc.
Date of Submission	September 30, 2011, received October 3, 2011
PDUFA Goal Date	August 3, 2012
Proprietary Name / Established (USAN) names	Injectafer (ferric carboxymaltose)
Dosage forms / Strength	Injection (single-use vials (b) (4) 750 mg iron/15 mL
Proposed Indication(s)	for the treatment of iron deficiency anemia
Recommended:	Complete Response

1. Introduction

Injectafer (iron carboxymaltose) is an iron formulation developed for parenteral administration. This 505(b)(1) application is submitted for the indication for "for the treatment of iron deficiency anemia". The proposed dosing is 15 mg/kg up to a maximum single dose of 750 mg of iron on two occasions separated by at least 7 days up to a cumulative dose of 1500 mg of iron delivered by intravenous infusion or injection.

Iron deficiency is the most common cause of anemia worldwide and is most often due to blood loss or chronic dietary insufficiency. Iron deficiency anemia occurs in hemodialysis patients due to destruction of red blood cells during dialysis, along with anemia secondary to renal disease.

The current submission is the second NDA application submitted by Luitpold Pharmaceuticals, Inc. for this product. An original NDA (22-054) for iron carboxymaltose (then referred to as Ferinject) was first submitted to the FDA on June 15, 2006 for treatment of iron deficiency anemia in: heavy uterine bleeding, postpartum, inflammatory bowel disease (IBD) and hemodialysis patients, employing a dose of up to 1000 mg elemental iron infusion as a single administration. The application received a non-approval action on July 9, 2007 because of an unfavorable benefit/risk relationship for the patients with iron deficiency anemia targeted for use of the product, mainly due to a mortality disadvantage observed for the drug in the overall development program.

The current submission of NDA 203565 proposes a broader indication and a lower dose and is intended to address the safety concerns that led to non-approval of NDA 22-054. The new NDA proposes the indication: "Injectafer is indicated for the treatment of iron deficiency anemia" and proposes a dose of 15 mg/kg body weight up to a maximum of 750 mg of iron on two occasions separated by at least 7 days up to a cumulative dose of 1500 mg of iron. The NDA includes two studies designed to assess cardiovascular safety ---one in patients with chronic renal failure (Protocol 1VIT09030 [REPAIR-IDA]) and one in subjects with iron deficiency anemia due to a broad range of etiologies (Protocol 1 VIT09031). Both of these studies employ the lower 750 mg dose. The application also includes three additional supportive trials 1VIT08019, 1 VIT08020 and 1VIT08021 using the 750 mg maximum single dose. These studies are reviewed and discussed in detail in the Clinical Review by Min Lu, M.D. (signed in DARRTS 6/8/2012).

The sponsor reports that ferric carboxymaltose (Ferinject) is approved in the European Union (2007) and is approved in 38 countries worldwide. The indication is specified as "for the treatment of iron deficiency (ID) when oral iron preparations are ineffective or cannot be used. The diagnosis must be based on laboratory tests. Ferinject is contraindicated for the treatment of anaemia not caused by ID (e.g., other microcytic anaemia) and in cases of iron overload, disturbances in iron utilization or known hypersensitivity to Ferinject or any of its excipients." Ferinject (50 mg iron/mL) can be administered by drip infusion or injection.

2. CMC/Device

The chemistry, manufacturing and controls (CMC) information in the application has been reviewed by S-C Lin, Office of New Drug Quality Assessment (ONDQA) (review signed in DARRTS June 8, 2012). Regarding the chemistry of the drug substance the review states that ferric carboxymaltose is an iron-carbohydrate complex. The review states:

> Although ferric carboxymaltose has not been used in approved drug products, it is not a new molecular entity (NME). A NME is a compound that contains an active moiety that has never been approved by FDA or marketed in the United States. For this drug substance, the active moiety is iron (III). There have been approved iron (III)-carbohydrate drug products on the market (e.g., iron dextran injection and iron sucrose injection) for which iron (III) is also the active moiety and the strengths of the products are expressed in terms of iron. Therefore, the drug substance is a new complex of iron rather than a NME.

The review indicates the drug product is a sterile brown solution for intravenous use and will be provided as (b) (4) 50 mg/mL solution in single-use vials. The review found the submitted stability data were adequate to support proposed 24-month expiration dating period for the drug product at the controlled room temperature.

The CMC review (S-C Lin) summarized the CMC findings stating:

> The CMC information of the drug substance was referenced to DMF 16967, which has been reviewed by this reviewer and found to be adequate. This reviewer has consulted the pharm/tox team (Dr. Brenda Gehrke, pharm/tox reviewer, and Dr. Haleh Saber, pharm/tox team leader) regarding the acceptability of the proposed limits for (b) (4) (b) (4) The drug substance specification, as revised in the 06-Jun-2012 amendment of the NDA, is adequate.
>
> Adequate data have been provided to ensure the quality of the drug product. The microbiology reviewer has determined that the drug product is acceptable from the microbiology perspective. The revised drug product specification, as submitted in the 23-Apr-2012 amendment, is adequate.

The review commented, however, that though the drug substance manufacturing and testing sites are acceptable, the establishment evaluation for Luitpold, the drug product manufacturer, was still pending in EES (Establishment Evaluation System). The review states:

> The Office of Compliance has not issued an overall recommendation for the inspections of the manufacturing and testing facilities for the drug substance and drug product. Therefore, this NDA may not be approved until a final acceptable recommendation is made by the Office of Compliance.

In a July 9, 2012 Memorandum the CMC reviewer (S-C Lin) updated the recommendation stating that the Office of Compliance had issued an overall withhold recommendation for the

application on July 5, 2012 and therefore "from a CMC perspective approval of NDA 203565 cannot be recommended until any related deficiencies are resolved."

A categorical exclusion from the preparation of an environmental assessment (ES) was requested by the sponsor and found to be adequate for the product.

3. Nonclinical Pharmacology/Toxicology

The non-clinical Pharmacology/Toxicology primary review was conducted by BJ Gehrke, Ph.D. (signed in DARRTS June 6, 2012). The review stated:

> Ferric carboxymaltose injection was originally submitted by Luitpold Pharmaceuticals Inc. under NDA 22054 on June 15, 2006 for the indication of treatment of iron deficiency anemia in heavy uterine bleeding, postpartum, inflammatory bowel disease and hemodialysis patients. A Not Approvable letter was issued on July 9, 2007 with clinical deficiencies. The nonclinical studies for Ferric carboxymaltose were reviewed during this initial submission of NDA 22054. Studies reviewed included pharmacology; safety pharmacology; pharmacokinetics; general toxicology studies including 13-week studies in rats and dogs; genetic toxicology; fertility, embryo-fetal and peri and postnatal development toxicology studies; and local tolerance studies. Carcinogenicity studies were not submitted nor are they needed per ICH S1A due to the short-term intermittent nature of the clinical dosing. There were no pharmacology/toxicology issues at that time, and approval was recommended for ferric carboxymaltose by the pharmacology/toxicology review team (Dr. Yash Chopra and Dr. Adebayo Laniyonu). The NDA was resubmitted on September 12, 2007 and a second Not Approvable letter was issued on March 11, 2008 with clinical deficiencies. Since the indication was changed from the original NDA, NDA 203565 was submitted on September 30, 2011 as a new NDA for Injectafer (ferric carboxymaltose) by Luitpold Pharmaceuticals Inc. for the indication of iron deficiency anemia. No additional pharmacology/toxicology studies are needed for the proposed indication and none were submitted to NDA 203565. The Applicant is cross-referencing the nonclinical data in NDA 22054.

Findings of the Pharmacology/Toxicology Review of the June 16, 2006 NDA 22-054 submission of ferric carboxymaltose (Y. Chopra, Ph.D., June 5, 2007) can be summarized as follows: The accumulation of the administered iron was 76% in red blood cells, 11% in liver, 2% in spleen and 1% in kidney. Repeat dose toxicity studies in rats and dogs showed iron deposition in liver, spleen, lymph nodes and kidneys. Single intravenous doses of 0.24 g/kg in dogs and 1 g/kg in rats were not lethal. The animal toxicity studies did not identify any treatment-related changes in vital signs or any signs of cardiovascular effects in rats and mice. In the 26-week chronic IV injection toxicity study in dogs at week 13 showed a dose-related decrease in heart rate and slight effect on QT interval in male animals but were normal at 26 weeks. There was some increase in blood pressure at 2 hours postdose. The drug was not genotoxic or mutagenic and exerted no adverse effects on fertility and reproductive parameters. Fetal malformations of cranial deformity with hydrocephaly in rabbits were found at a maternal toxic dose. Recommendation is made for designation of Pregnancy Category (b)(4).

Dr. Chopra's review concluded, "From the preclinical pharmacology and toxicology view point, VIT-45 should be approved."

Pharmacology/Toxicology review of the current NDA raised a concern regarding the proposed acceptance criteria levels of the heavy metal impurities (b) (4) in the drug substance, which were much higher than the permitted daily exposure values for these metals. Also, for ferrous iron (b) (4) proposed levels were higher than the permitted daily exposure limits listed in the USP and EMA guidelines. Comments regarding these deficiencies were sent to the sponsor on May 10, 2012 and a response was received on May 16, 2012. The sponsor revised the acceptance criteria for (b) (4) to the following:

Heavy metal	Acceptance criteria in DS (µg/g Fe)	Level of heavy metal (µg) per iron dose of 750 mg (µg)	USP Parenteral PDE (µg/day)
(b) (4)			

The response provided justification for the proposed new criteria, which still exceeded the permitted daily exposure values. Justification mainly focused on the periodic short-term use of the drug. The Dr. Gehrke's review states:

For the new acceptance criteria, the levels of (b) (4) present in a single 750 mg dose of iron are still higher than the USP permitted daily exposure recommendations. It is noted that discussions on safety-based acceptable levels of heavy metals are ongoing as part of the ICH Q3D discussions. However, for the metals listed above, the acceptance criteria provided above are acceptable for the following reasons.

(b) (4)

Thus, the revised drug substance acceptance criteria for (b) (4) (b) (4) for ferric carboxymaltose are acceptable from a pharmacology/toxicology perspective.

The review noted that discussions on safety-based acceptable levels of heavy metals are ongoing as part of the ICH Q3D discussions.

Regarding (b) (4) the sponsor referred to the fact that the proposed limit for (b) (4) in ferric carboxymaltose of (b) (4)-fold less than the current calculated limit allowed for Venofer (iron sucrose injection). Based on this justification the review found the acceptance criteria acceptable from a pharmacology/toxicology perspective. The review concluded that there were no pharmacology/toxicology issues which precluded approval of the drug for the proposed indication.

The review included comments and recommendations for labeling. Pharmacologic class as "iron replacement product" was confirmed as consistent with that for the other intravenous iron products.

A Memorandum from JK Leighton, Ph.D., Acting Director division of Hematology Oncology Toxicology, Office of Hematology and Oncology Products concurred with Dr. Gehrke's conclusion that Injectafer may be approved and that no additional non-clinical studies are needed for the proposed indication.

4. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology Review was conducted by BA Habetemariam (signed in DARRTS June 21, 2012). The review comments: "The clinical pharmacology aspects of FCM were reviewed previously and are available in DARRTS (C John, 5/30/2007). The clinical pharmacology aspects of the NDA were found to be acceptable during the original NDA 22-054 submission and no specific clinical pharmacology studies were requested." The Clinical Pharmacology review for this new NDA focused on review or the findings of a breast milk pharmacokinetic study that was submitted to NDA 22-054 on June 15, 2006 but which was not commented on in the Clinical Review at that time but findings were described in the proposed labeling.

The breast milk study was conducted as a sub-study of a phase 3 study (1VIT-IV-CL-009) comparing intravenous ferric carboxymaltose (FCM) to oral iron sulfate in women with post-partum anemia. It collected breast milk iron level data from 25 subjects (11 following ferric carboxymaltose (FCM); 15 following oral iron sulfate). Breast milk pharmacokinetic data for the study were not submitted at the time of the Clinical Pharmacology review. However, the Clinical Pharmacology Review agreed with the sponsor's conclusion, based on the sponsor's analyses in the clinical study report, that the highest iron level measured in the breast milk sub-study was well below 40 mg.

The sponsor provided discussion that the US recommended dietary allowance for iron for infants from birth to age 6 months is 40 mg iron per day and that therefore the highest concentration of breast milk iron measured in the study would result in iron intake well below the recommended maximum US RDA iron intake. Clinical Pharmacology deferred to Clinical regarding appropriate threshold of iron levels in breast milk. In the Clinical Pharmacology review Dr. Habtemariam noted that the sponsor will submit breast milk PK data at a later date and an addendum will be made to the Clinical Pharmacology Review. The review concluded,

"From reviewer's perspective, the submitted clinical study report provides sufficient information to complete the labeling for injectafer."

No post-marketing requirements were recommended.

5. Clinical Microbiology

Product Quality Microbiology Review by SE Langille, Ph.D., (signed in DARRTS May 8, 2012) noted that Injectafer will be (b) (4) (b) (4) and no deficiencies were identified. The review recommended approval from a product quality microbiology perspective and had no recommendations for post-marketing.

6. Clinical/Statistical- Efficacy

The sponsor conducted two pivotal studies in support of this application, 1VIT09031 and 1VIT09031. Both were randomized, open-label, active controlled studies. The detailed Clinical Review of this application has been conducted by Dr. M. Lu (signed in DARRTS June 8, 2012). Secondary Clinical Review was conducted by Dr. KM Robie Suh (review signed in DARRTS July 20, 2012). The Statistical Review of the application was conducted by K-Y Lee (review signed in DARRTS June 28, 2012). Please see these reviews for detailed presentation of the clinical efficacy findings.

In the Clinical Review Dr. Lu describes the study design and efficacy findings of the review as follows:

Two randomized controlled pivotal trials (1VIT09031 and 1VIT09030) were conducted to support the efficacy of Injectafer with the proposed dose regimen of 15 mg/kg with the maximum individual dose of 750 mg and a total dose of 1,500 mg. Study 1VIT09031 was conducted in patients with iron deficiency anemia who had an inadequate response to oral iron treatment, who were intolerant to oral iron during the 14-day run-in period, or who were deemed unsuitable by the Investigator for the oral iron, mainly due to low hemoglobin level with or without co-morbidities. Study 1VIT09030 was conducted in patients with non-dialysis dependent chronic kidney disease (NDD-CKD). Both clinical studies were randomized, open-label, controlled studies. In Study 1VIT09031, oral iron was used as control in patients who had an inadequate response to oral iron treatment in Cohort 1 and other IV iron products (mostly Venofer) were used as control in patients who were intolerant to oral iron in Cohort 2. In Study 1VIT09030, Venofer was used as control in patients with NDD-CKD. The primary efficacy endpoint was the mean change from baseline to the highest observed hemoglobin observed anytime between baseline and Day 35 or time of intervention in Study 1VIT09031 and between baseline and Day 56 or time of intervention in Study 1VIT09030.

In Study 1VIT09031, the results show that the mean increase in hemoglobin from baseline to the highest value between baseline and Day 35 or time of intervention in the Injectafer group was statistically significantly greater than that in the oral iron group in Cohort 1 (1.57 g/dL vs. 0.80 g/dL, $p<0.01$) and also higher than that in the IV standard care group (2.90 g/dL vs. 2.16 g/dL, $p<0.01$) in Cohort 2. In Study 1VIT09031, the mean increase in hemoglobin from baseline to the highest value between baseline and Day 56 or time of intervention in the Injectafer group was non-inferior to Venofer (1.13 g/dL vs. 0.92 g/dL, treatment difference 0.21 g/dL [95% CI 0.13-0.28 g/dL]). The results from the secondary efficacy endpoints analyses including hemoglobin response and iron indices were consistent with the primary efficacy analysis results in both studies. The results from subgroup analyses including baseline hemoglobin level and etiology of iron deficiency anemia in Study 1VIT09031 and baseline hemoglobin, EPO use and CKD stage in Study 1VIT09030 were all consistent with the results from the primary efficacy endpoint analyses.

The Statistical Review (K-Y Lee, review signed in DARRTS June 28, 2012) examined the results and analyses for Studies 1VIT09031 and 1VIT09030 in detail. The primary efficacy analyses for these studies from the Statistical Review are shown below.

For Study 1VIT09030:

Table 6 : Mean Change in Hemoglobin from Baseline to the Highest Value between Baseline and Day 56 (or time of intervention): mITT Population (Study 1VIT9030)

	FCM (N=1249)	Venofer (N=1244)
Baseline		
Mean (SD)	10.31 (0.83)	10.33 (0.83)
Highest		
Mean (SD)	11.44 (1.19)	11.25 (1.08)
Change		
Mean (SD)	1.13 (1.04)	0.92 (0.92)
Difference (95% CI)	0.21 (0.13, 0.28)	

For the primary efficacy analysis of Study 1VIT09030 the Statistical Review indicated that the results showed Injectafer was non-inferior to Venofer in mean change in hemoglobin for the analysis. The review also found that with regard to the proportion of patients having an increase in hemoglobin $\geq$1.0 g/dL from baseline to the end of study period, the result for the Injectafer arm was superior to that for the Venofer arm in this study.

For Study 1VIT09031:

Table 12: Mean Change in Hemoglobin from Baseline to the Highest Value between Baseline and Day 35 (or time of intervention) (mITT) (Cohort 1 in Study 1VIT9031)

	FCM (N=244)	Oral Iron (N=251)
N	244	251
Baseline		
Mean (SD)	10.59 (1.01)	10.62 (1.03)
Highest		
Mean (SD)	12.16 (1.11)	11.42 (1.18)
Change		
Adjusted Mean*	1.52	0.76
Adjusted Difference (95% CI)*	0.76 (0.59, 0.93)	
p-value *	<0.0001	

*:ANCOVA with treatment and etiology of IDA as fixed factors and baseline hemoglobin as a covariate.

Table 13: Mean Change in Hemoglobin from Baseline to the Highest Value between Baseline and Day 35 (or time of intervention) (mITT) (Cohort 2 in Study 1VIT9031)

	FCM (N=245)	IV SC (N=237)
Baseline		
Mean (SD)	9.12 (1.60)	9.02 (1.47)
Highest		
Mean (SD)	12.02 (1.22)	11.17 (1.26)
Change		
Adjusted Mean*	2.93	2.12
Adjusted Difference (95% CI)*	0.81 (0.61, 1.00)	
p-value *	<0.0001	

*:ANCOVA with treatment and etiology of IDA as fixed factors and baseline hemoglobin as a covariate.

For the primary efficacy analysis of Cohort 1 in Study 1VIT09031 the Statistical Review indicated that the results showed Injectafer was statistically superior to oral iron in the mean hemoglobin change from baseline to the highest value between baseline and Day 35 (or time of intervention) after adjusting for etiology. For the primary efficacy analysis of Cohort 2 in the study the Statistical Review indicated that the results showed Injectafer was statistically superior to intravenous standard of care (SC) iron administration in mean hemoglobin change from baseline to the highest value between baseline and Day 35 (or time of intervention) after adjusting for etiology. The review found that for all supportive efficacy endpoints in Study 1VIT09031, for Cohort 1 and Cohort 2, results for Injectafer were superior to those for the oral iron arm in Cohort 1.

Overall, regarding efficacy the Statistical Review concluded that:

The observed mean changes in hemoglobin from baseline to the highest values during the study period demonstrated clinical benefit in subjects who had iron deficiency anemia impaired renal function with non-dialysis dependent chronic kidney disease (CKD) (1VIT9030) and oral iron subjects who had an unsatisfactory response to a 14-day oral iron run-in (1VIT9031).

7. Safety

The detailed Clinical Review of this application has been conducted by Dr. M. Lu (signed in DARRTS June 8, 2012). Secondary Clinical Review was conducted by Dr. KM Robie Suh (review signed in DARRTS July 20, 2012). The Statistical Review of the application was conducted by K-Y Lee (review signed in DARRTS June 28, 2012). Please see these reviews for detailed presentation of the clinical safety findings.

In the Clinical Review Dr. Lu finds the safety assessments provided in the application are adequate. Regarding safety findings the Clinical Review (M. Lu, M.D. (signed in DARRTS June 8, 2012) summarizes the exposure and mortality findings as follows:

> A total of 1775 subjects have received the proposed Injectafer dosing regimen of 15mg/kg with the maximum of single dose of 750 mg and maximum total dose of 1500 mg in two pivotal clinical studies. The majority of patients have received 750 mg dose for 2 doses. A total of 2566 subjects have been exposed to Injectafer as a maximum single dose of 750 mg with the different total doses. A total of 6679 subjects have been exposed to Injectafer with different dosing regimens in the Phase 2/3 development program.
>
> The mortality rates were similar between Injectafer for the proposed dosing regimen and the comparators in pooled analysis of the two pivotal studies (16/1775, 0.9% vs. 21/1783, 1.2%) and were also similar between Injectafer with the maximum single dose of 750 mg with the different total doses and the comparator in pooled analysis of the five clinical studies (17/2566, 0.7% vs. 22/2590, 0.8%). For all completed studies, the overall mortality rate was 0.5% (33/6679) in the Injectafer-treated patients and 0.6% (30/5394) in comparator-treated patients.

In the two pivotal trials, no significant differences were found between Injectafer and comparator for the pre-specified primary cardiovascular endpoint (which included death, myocardial infarction, stroke, unstable angina, congestive heart failure, hypertension and hypotension). However, rates of hypertensive events were found to be significantly higher in the Injectafer group as compared to the Venofer group or the pooled comparator group for the two pivotal studies (6.0%, 4.1% and 3.5%, respectively). Among patients receiving Injectafer in the two pivotal studies the most common treatment-emergent adverse events leading to study drug discontinuation were flushing and hypertension (0.5% and 0.6% of patients, respectively).

See Dr. Lu's Clinical Review for a detailed description and summary of the adverse events seen with Injectafer for the various safety analysis populations of patients exposed and doses used.

Regarding foreign post-marketing experience the Clinical Review indicates that 8 spontaneous reports of death have been received since marketing began and notes that the European Union Summary of Product Characteristics (SPC) has been updated. The review states:

European Union Summary of Product Characteristics (SPC) has been updated to include the addition of "anaphylactoid reaction, which may be potentially fatal" in the Special Warnings and Precautions for Use Section and amending the Undesirable Effects section to include "hypersensitivity including anaphylactoid reactions" and "dyspnea". A variation was submitted during the period of Periodic Safety Update Report (PSUR) for Ferinject in February 2011 adding hypertension to the SPC; it is still under review. Areas of special interest including hyperkalemia, urinary tract infection, bronchitis, hypertension, bilirubin increased, infusion site reactions, cardiac disorders, hypersensitivity, hypophosphatemia, hemosiderosis, and fatal events continue to be monitored and presented in the PSURs.

The Clinical Review concludes that the overall benefit of Injectafer treatment outweighs the risk for the intended population and recommends:

From a clinical perspective, Injectafer should be approved for the indication for the treatment of iron deficiency anemia in patients who are intolerant to oral iron or have had unsatisfactory response to oral iron and in patients with non-dialysis dependent chronic kidney disease.

Regarding labeling the review recommends that the labeling should include WARNINGS AND PRECAUTIONS for hypersensitivity, hypertensive reactions and iron overload associated with Injectafer treatment. As for other intravenous iron products, the risk of hypersensitivity reactions under WARNINGS AND PRECAUTIONS should be highlighted in bold letters.

The Secondary Medical Team Leader review of the application concurs with the conclusions and recommendations for regulatory action in Dr. Lu's Clinical Review.

8. Advisory Committee Meeting

There was no advisory committee meeting for this application.

9. Pediatrics

No pediatric patients were studied for the current NDA. The sponsor has requested a waiver for conducting pediatric studies in patients less than (b)(4) years of age, "due to logistical challenges associated with subjects of this age range" and citing previous pediatric experience with its other intravenous iron product, Venofer (iron sucrose), recruiting patients from birth to <2 years of age into Phase III trials. The sponsor proposes a PK study and an efficacy and safety study in older pediatric patients.

The Clinical Review (M Lu, M.D., June 8, 2012) states the following:

The applicant requested a deferral of pediatric studies in (b)(4) and 17 years of age group under PMRs and requested a waiver of a pediatric study in the 0-(b)(4) years of age group to meet the requirements of Pediatric Research Equity Act (PREA). The proposed pediatric studies in (b)(4) and 17 years of age group include one pharmacokinetic/pharmacodynamic study and one safety and efficacy study in pediatric patients with iron deficiency anemia. The applicant proposed to submit full pediatric study protocols within one year of approval and recruitment will begin within the first 18 months after the NDA is approved with the final study report being submitted on or before December 31, 2016. These requests should be granted.

The labeling was reviewed and recommendations for the labeling were made with regard to pregnancy, nursing mothers and pediatric use by the Pediatric and Maternal Health Staff (C Ceresa, Pharm.D., final signature in DARRTS July 2, 2012).

10. Other Relevant Regulatory Issues

The Office of Scientific Investigations (OSI) inspected two (U.S.) clinical investigator sites from Study 1VIT09030 and two (U.S.) clinical investigator sites from Study 1VIT09031 and the sponsor. The Clinical Inspection Summary (AJ Orencia, M.D., Division of Good Clinical Practice Compliance, OSI, signed in DARRTS June 28, 2012) states, "Based on review of inspectional findings for these clinical investigators and the Sponsor, the study data collected appear generally reliable in support of the requested indication." The review notes that observations stated in the review are based on the preliminary communications from the field investigators and if conclusions change significantly upon receipt of the final establishment inspection reports (EIRs), an inspection summary addendum will be generated.

The Clinical Review (M Lu, M.D., final signature in DARRTS June 8, 2012) did not identify any conflict of interest issues that would be expected to impact the overall study conclusions for clinical investigators in studies 1VIT09030 or 1VIT09031. In supporting studies 2 investigators and 1 steering committee member had received consulting fees of about $27,500 to $30,000.

The Division of Professional Drug Promotion (DPPP) reviewed the draft labeling and provided comments for the Clinical Studies (Section 14) of the labeling (J Dvorsky, review memorandum in DARRTS June 18, 2012).

Labeling review by the Division of Medication Error Prevention and Analysis (DMEPA) was conducted by K DeFronzo (review signed in DARRTS June 7, 2012). The review concluded that the proposed labeling could be improved to increase the readability and prominence of important information on the label to promote the safe use of the product and provided recommendations for the package insert, the container labeling and carton labeling, and the box labeling.

The Division of Medication Error Prevention and Analysis (DMEPA) (K DeFronzo, final signature in DARRTS February 23, 2012) reviewed the proposed proprietary name, Injectafer, and found it acceptable from both a promotional and safety perspective. Final proprietary

name review was conducted by SK Vee, Pharm.D., Division of Medication Prevention and Analysis (DMEPA) (signed in DARRTS June 22, 2012). The review for the proposed name, Injectafer, did not identify any vulnerabilities that would result in medication errors with any additional names noted in this review. DMEPA had no objection for the name and the review concluded that the name Injectafer is acceptable. Re-review of the name would be required if approval of the NDA is delayed beyond 90 days from the date of the review.

11. Labeling

The sponsor included proposed labeling in the submission. Exact wording for the labeling is being developed by the review team incorporating the recommendations from each of the review disciplines and consulting review divisions.

12. Recommendations/Risk Benefit Assessment

Based on the Clinical and Statistical Reviews of the submitted studies and materials, particularly the pivotal efficacy and safety studies 1VIT09030 and 1VIT09031, the sponsor has provided adequate evidence to show a favorable benefit-to-risk assessment for Injectafer (iron carboxymaltose) for treatment of iron deficiency anemia in the studied populations of adult patients with iron deficiency anemia using a dose of 15 mg/kg up to a maximum single dose of 750 mg of iron on two occasions separated by at least 7 days up to a cumulative dose of 1500 mg of iron delivered by intravenous infusion or injection. Subjects in Study 1VIT09030 were patients with iron deficiency anemia and non-dialysis dependent chronic kidney disease. Subjects in Study 1VIT09031 had iron deficiency anemia of any etiology (about half were women with heavy uterine bleeding) and were intolerant of or had an unsatisfactory response to oral iron. The wording the sponsor has proposed for the indication in the label should be revised to better reflect the populations of patients studied in the pivotal trials.

Evaluation of safety in the pivotal studies showed similar mortality rates for Injectafer and the comparator. No significant difference between treatment arms was observed for the pre-specified primary cardiovascular composite safety endpoint in the two studies.

Review of the application did not reveal any deficiencies that would preclude approval from a non-clinical, clinical pharmacology, or clinical perspective. However, for Chemistry, Manufacturing and Controls (CMC), the Office of Compliance has issued an overall withhold recommendation for this application. Accordingly, from a CMC perspective, approval of the NDA cannot be recommended until any related deficiencies are resolved (Memorandum, S-C Lin, signed in DARRTS July 9, 2012).

The sponsor’s proposed labeling has been reviewed and edited by all appropriate review disciplines and tentative revised draft labeling has been formulated.

Regarding possible post-marketing study requirements, the review recommends that a waiver for pediatric studies required under PREA for the indication be granted for studies of Injectafer in patients less than (b)(4) years of age, because of too few children with disease to study. Pediatric studies in older children may be deferred; however, protocols for proposed studies should be submitted for review.

No other post-marketing studies are recommended at this time.

In conclusion, it is recommended that a Complete Response letter should be issued for this application due to the overall withhold recommendation from the Office of Compliance. Deficiencies related to the withhold recommendation must be resolved prior to approval. No other deficiencies are identified which would prevent approval.

The tentative revised draft labeling generated by the review team may be forwarded to the sponsor with the Complete Response letter for information purposes to facilitate the sponsor's revision of the proposed label if and when a response to the CR letter is submitted.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATHY M ROBIE SUH
07/21/2012

M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: July 16, 2012

From: Kathy M. Robie-Suh, M.D., Ph.D.
Medical Team Leader, Hematology
Division of Hematology Products
Office of Hematology and Oncology Products, CDER

Subject: Medical Team Leader Secondary Clinical Review
NDA 203565, submitted 9/30/2011 (received 10/3/2011)
Injectafer (VIT-45, ferric carboxymaltose) for the treatment of iron deficiency anemia
Sponsor: Luitpold Pharmaceuticals, Inc.

To: NDA 203565

This application seeks approval of Injectafer (ferric carboxymaltose) for the broad indication of the treatment of iron deficiency anemia. The proposed dosing is 15 mg/kg up to a maximum single dose of 750 mg of iron on two occasions separated by at least 7 days up to a cumulative dose of 1500 mg of iron delivered by intravenous infusion or injection.

The primary clinical review of this application has been conducted by Dr. M. Lu (Clinical Review signed in DARRTS 6/8/2012).

Background:
Iron deficiency is the most common cause of anemia worldwide. The majority of the total body iron is localized in hemoglobin in red blood cells. Because the body has a tightly regulated mechanism of absorption of dietary iron and no mechanism for excreting iron, iron deficiency anemia is most often due to blood loss or chronic dietary insufficiency. Iron deficiency anemia occurs in hemodialysis patients due to destruction of red blood cells during dialysis, along with anemia secondary to renal disease.

Injectafer (iron carboxymaltose) is an iron formulation developed for parenteral administration to treat iron deficiency anemia. An original NDA (22-054) was submitted on June 15, 2006 for the drug (then referred to as Injectafer) for treatment of iron deficiency anemia in: heavy uterine bleeding, postpartum, inflammatory bowel disease (IBD) and hemodialysis patients, employing a dose of up to 1000 mg elemental iron infusion as a single administration. The application received a non-approval action on July 9, 2007 because of an unfavorable benefit/risk relationship for the patients with iron deficiency anemia targeted for use of the product, particularly with regard to a mortality disadvantage for the drug observed in the overall development program. On September 30, 2007 the sponsor responded with some additional data in patients with chronic renal failure on hemodialysis and a proposed narrowed

target patient population (iron deficiency anemia in women with heavy uterine bleeding and postpartum women with iron deficiency anemia). During the review cycle the sponsor further revised the indicated population to iron deficiency anemia in women with heavy uterine bleeding and postpartum women with iron deficiency anemia who are intolerant to oral iron and had an unsatisfactory response to oral iron or required rapid and reliable repletion of iron. The proposed maximum single dose was the lower of 1000 mg or 15 mg/kg. Review of the resubmission, including discussion of the application at a meeting of the Drug Safety and Risk Management Advisory Committee (February 1, 2008), concluded that the safety risk for mortality had not been sufficiently characterized to adequately label the product for marketing, citing the small numbers of heavy menstrual bleeding and postpartum women studied, the lack of data in these women who are intolerant/refractory to oral iron, and concern for possible excessive iron dose during a single administration with the proposed dosing regimen for the drug. Accordingly, a non-approval action was taken on the application on March 11, 2008. For additional detail regarding prior review of ferric carboxymaltose injection for iron deficiency anemia see my secondary reviews for NDA 22054 signed in DARRTS 6/29/2007 and 3/11/2008 and the additional clinical and other reviews referenced therein.

The current submission of NDA 203565 is a new application that is intended to address all the concerns in the March 11, 2008 non-approval letter for NDA 22-054. The new NDA proposes the indication: "Injectafer is indicated for the treatment of iron deficiency anemia" and proposes a dose of 15 mg/kg body weight up to a maximum of 750 mg of iron on two occasions separated by at least 7 days up to a cumulative dose of 1500 mg of iron. The NDA includes two studies designed to assess cardiovascular safety ---one in patients with non-dialysis dependent chronic renal failure (Protocol 1VIT09030 [REPAIR-IDA]) and one in subjects with iron deficiency anemia due to a broad range of etiologies and who were intolerant to or had unsatisfactory response to oral iron (Protocol 1 VIT09031). Both of these studies employed the lower 750 mg maximum single dose. The application also includes safety results from three additional supportive trials 1VIT08019, 1 VIT08020 and 1VIT08021 using the 750 mg maximum single dose.

The sponsor reports that ferric carboxymaltose (Ferinject) was approved 7/6/2007 in The Netherlands and first launched in the European Union in Germany in November 2007 (IND 63243 Annual Report received 3/24/2012, covers period 1/16/2011 to 1/15/2012). The Annual Report states the indication is "for the treatment of iron deficiency (ID) when oral iron preparations are ineffective or cannot be used. The diagnosis must be based on laboratory tests. Ferinject is contraindicated for the treatment of anaemia not caused by ID (e.g., other microcytic anaemia) and in cases of iron overload, disturbances in iron utilization or known hypersensitivity to Ferinject or any of its excipients." Ferinject (50 mg iron/mL) can be administered by drip infusion or injection. Ferinject is currently approved in 38 countries worldwide.

Several iron products are currently marketed in the U.S. for treatment of iron deficiency anemia. These include oral iron as ferrous sulfate, which is most commonly used. Iron products approved for intravenous administration for treatment of iron deficiency anemia include: sodium ferric gluconate complex (Ferrlecit), iron sucrose (Venofer), iron dextran (INFeD, Dexferrum), and Feraheme (ferumoxytol). Maximum dose among these products in iron deficient patients with chronic kidney disease (on hemodialysis or not on hemodialysis) is

510 mg of elemental iron administered intravenously at a rate of up to 30 mg/sec (Feraheme) (approved 6/30/2009). For Venofer in patients on hemodialysis maximum dose is 100 mg of elemental iron over 2-5 minutes and in non-dialysis dependent chronic renal failure patients is 200 mg elemental iron over 2-5 minutes. The Venofer labeling indicates there is limited experience with Venofer 500 mg given over 3.5-4 hours in non-dialysis dependent renal failure patients; but hypotension occurred in 2 of 30 patients treated. In peritoneal dialysis patients Venofer has been given as two 300 mg infusions over 1.5 hours separated by 2 weeks and followed after an additional 2 weeks by a 400 mg infusion given over 2.5 hours. Recommended dose of Ferrlecit is 125 mg elemental iron. Venofer, Ferrlecit and Feraheme labels carry a bolded Warning for hypersensitivity reactions. Maximum recommended dose of iron dextran is 100 mg daily to total prescribed dose, with dose being given not faster than 50 mg iron/min. Because of concern for anaphylactic reactions, for iron dextran, INFeD and Dexferrum labels carry a Boxed Warning for anaphylactic reactions and administration of a test dose is recommended prior to administration of a therapeutic dose.

Findings of the Clinical Review:
The sponsor conducted two pivotal studies in support of this application, 1VIT09031 and 1VIT09031. Both were randomized, open-label, active controlled studies. These trials are described briefly below. For a detailed description of the study and presentation of the study results see the Clinical Review by M. Lu, M.D. (signed in DARRTS 6/8/2012) and the Statistical Review by K Y Lee, Ph.D. (signed in DARRTS 6/28/2012).

Study 1VIT09031:
Study 1VIT09031 was a multicenter, randomized, open-label trial conducted from 9/15/2009 to 3/22/2011 in 84 sites in the U.S. The main study objective was to demonstrate the efficacy and safety of FCM compared to oral iron in subjects with iron deficiency anemia who have shown an unsatisfactory response to oral iron. The study enrolled two cohorts of adult patients with iron deficiency anemia [IDA; defined as screening visit hemoglobin $\leq$11 g/dL, serum ferritin $\leq$100ng/mL or $\leq$300 ng/mL when transferrin saturation (TSAT) is $\leq$30%] as follows:

- Cohort 1: patients with IDA who were found to have an inadequate response to a 14 day oral iron run-in period (defined as hemoglobin increase <1g/dL from baseline despite $\geq$67% compliance), and continued serum ferritin $\leq$100ng/mL or $\leq$300 ng/mL when TSAT is $\leq$30%
- Cohort 2: patients with IDA who were poorly tolerant or inappropriate for oral iron treatment, such as, documented severe gastrointestinal or other symptoms due to oral iron and unresponsive to reduced dose during the 14-day run-in period or whose physicians feel are inappropriate for a 14 day course of oral iron. As for Cohort 1, patients who complete the 14 day run-in period must have hemoglobin increase <1g/dL from baseline despite $\geq$67% compliance), and continued serum ferritin $\leq$100ng/mL or $\leq$300 ng/mL when TSAT is $\leq$30%

Following the run-in/qualifying phase, eligible patients from Cohort 1 were randomized to either ferric carboxymaltose (FCM) 15mg/kg to a maximum of 750 mg per dose administered on Days 0 and 7 (total maximum cumulative dose of 1500 mg) as an undiluted IV push injection at 100 mg/min or to ferrous sulfate 325 mg orally three times daily for an additional

14 days. For Cohort 2 eligible patients were randomized to either FCM as described for Cohort 1 or IV standard of care (other IV iron) as determined by the study site physician. The primary efficacy analysis for the study was comparison for Cohort 1 of the mean increase from baseline to the highest observed hemoglobin value (baseline to Day 35 or time of intervention) for patients randomized to FCM as compared to for patients randomized to an additional 14 days of oral iron. For Cohort 1 the study also aimed to assess the safety and tolerability of FCM as compared to oral iron after 120 days. For Cohort 2 the study aimed to assess the safety and tolerability of FCM as compared to IV iron standard of care after 120 days.

Important exclusion criteria for both cohorts included: requirement for dialysis for treatment of chronic kidney disease (CKD); receipt of IV iron during 10 days prior to screening; treatment with off-label regimen of erythropoiesis stimulating agent (ESA), receipt of red blood cell transfusion, radiotherapy or chemotherapy, surgery requiring anesthesia, during the 30 days prior to screening or planned during study period; hemochromatosis or other iron storage disorders; pregnancy; life expectancy less than 6 months. For patients receiving ESAs dose must be stable ($\pm$20%) 4 wks prior to consent and not increase during study.

Patients were to return on Day -7 (during run-in) for assessment of compliance and oral iron tolerance. Following randomization patients were to return on Days 7, 14 and 35 for assessment of efficacy, safety evaluation (adverse events, laboratory assessment). Telephone follow-up was conducted at Day 90 and final follow-up visit at Day 120 for adverse reactions.

Demographics and Disposition: Among 1497 patients who received oral iron during the run-in period, 46.7% were randomized. The randomized cohorts were: Cohort 1 (250, FCM; 257, oral iron); Cohort 2 (253, FCM; 251, IV standard care (IV SC) [i.e., other IV iron]). Among the 498 subjects randomized in Cohort 2, about 67.6% were deemed inappropriate for oral iron by physician (i.e., did not receive oral iron run-in).

Demographics and important baseline characteristics of the 997 patients who were randomized and received any study drug during the randomized treatment phase of the study are summarized in the following table:

Study 1VIT09031: Demographics and Important Baseline Characteristics

Baseline Characteristic	Cohort 1		Cohort 2	
	FCM N=246	Oral iron N=253	FCM N=253	Other IV iron N=245
Age (yrs)				
Mean (SD)	43.1 (17.18)	43.5 (17.71)	43.6 (16.88)	42.6 (15.51)
Median	41	41	41	42
$\leq$65	214 (87.0%)	218 (86.2%)	220 (87.0%)	222 (90.6%)
Gender				
Female	233 (94.7%)	238 (94.1%)	239 (94.5%)	231 (94.3%)
Male	13 (5.3%)	15 (5.9%)	14 (5.5%)	14 (5.7%)
Race				
African American	95 (38.6%)	98 (38.7%)	63 (24.9%)	62 (25.3%)
Asian	2 (0.8%)	1 (0.4%)	0	3 (1.2%)
Caucasian	67 (27.2%)	79 (31.2%)	135 (53.4%)	136 (55.5%)

Hispanic	79 (32.1%)	69 (27.3%)	51 (20.2%)	41 (16.7%)
Other	3 (1.2%)	6 (2.4%)	4 (1.6%)	3 (1.2%)
Weight (kg)				
n	246	253	252	245
Mean (SD)	82.77 (22.449)	84.23 (24.764)	79.50 (20.442)	84.69 (25.929)
Median	79.4	79.4	77.5	78.5
BMI (kg/m^2)				
n	246	253	252	245
Mean (SD)	31.23 (8.372)	31.62 (8.491)	29.71 (7.585)	31.30 (8.883)
Median	29.5	30.1	28.5	29.5
Etiology of IDA				
HUB	126 (51.2%)	124 (49.0%)	111 (43.9%)	109 (44.5%)
GI disorders	26 (10.6%)	27 (10.7%)	59 (23.3%)	56 (22.9%)
Other	94 (38.2%)	102 (40.3%)	83 (32.8%)	80 (32.7%)
Baseline hemoglobin				
Mean (SD)	10.59 (1.006)	10.60 (1.064)	9.11 (1.601)	9.02 (1.460)
Median	10.6	10.8	9.2	9.1
Minimum, maximum	6.9, 13.7	6.4, 13.3	3.4, 13.2	4.5, 12.3
Baseline TSAT (%)				
Mean (SD)	22.11 (14.844)	22.42 (15.112)	11.48 (12.188)	10.32 (9.707)
Median	19	20	7	7
Minimum, maximum	2, 78	2, 84	2, 96	1, 53
<20%	129 (52.4%)	129 (51.0%)	208 (82.2%)	213 (86.9%)
Baseline Ferritin (ng/mL)				
Mean (SD)	31.30 (67.712)	28.20 (39.192)	25.85 (63.840)	14.89 (29.260)
Median	15.8	16.2	7.8	6.1
Minimum, maximum	1.0, 891.4	1.9, 325.6	0.5, 556.7	1.0, 279.3
<100 ng/mL	233 (94.7%)	240 (94.9%)	238 (94.1%)	241 (98.4%)
ESA Use				
No	246 (100.0%)	253 (100.0%)	248 (98.0%)	240 (98.0%)
Yes	0	0	5 (2.0%)	5 (2.0%)
Presence of Cardiac risk factors:				
Any	100 (40.7%)	107 (42.3%)	103 (40.7%)	104 (42.4%)
Age >75 yrs	16 (6.5%)	19 (7.5%)	14 (5.5%)	12 (4.9%)
Prior hx CV disease	13 (5.3%)	17 (6.7%)	24 (9.5%)	18 (7.3%)
Current smoker	14 (5.7%)	17 (6.7%)	25 (9.9%)	21 (8.6%)
Hypertension[a]	72 (29.3%)	77 (30.4%)	65 (25.7%)	70 (28.6%)
Hyperlipidemia[a]	35 (14.2%)	43 (17.0%)	36 (14.2%)	38 (15.5%)
Diabetes	34 (13.8%)	48 (19.0%)	25 (9.9%)	28 (11.4%)

SD=standard deviation; [a] or meds for

Reviewer's table based on data from sponsor's table in study report for 1VIT09031

The vast majority of patients (94%) were women and the mean age was about 43 years. About 38% of patients in Cohort 1 were African-American, followed closely by Hispanic and Caucasian in roughly equal numbers (about 30% each). Most patients in Cohort 2 were Caucasian (54%). In Cohort 1 about 71% of patients had baseline hemoglobin of 10.1g/dL or greater, while in Cohort 2 about 49% of patients had baseline hemoglobin of 9 or less. Among patients who received oral iron during the run-in period and were subsequently enrolled in the randomized period the mean change in hemoglobin during the run-in phase was 0.4 g/dL (median 0.35g/dL) for patients subsequently randomized in Cohort 1 and 0.3 g/dl (median, 0.2 g/dL) for patients subsequently randomized in Cohort 2. Approximately 54% of patients in Cohort 1 and 74% of patients in Cohort 2 had previous history of iron therapy. Approximately

25% of patients in Cohort 1 and 22% of patients in Cohort 2 had Cardiovascular risk category of 2 or worse.

The following table summarizes disposition of subjects enrolled in the study.

Study 1VIT09031: Disposition of Subjects (all Randomized)

	Cohort 1		Cohort 2		
	Group A: FCM	Group B: Oral Iron	Group C: FCM	Group D: IV SC	Total
Subjects Received Oral Iron During Run-In	249	258	100	92	699/798[a]
Subjects Did Not Receive Oral Iron During Run-In	0	0	154	158	312
Subjects Randomized	250	257	253	251	1011
Subjects Treated (Safety Population)	246	253	253	245	997
mITT Population[b]	244 (99.2%)	251 (99.2%)	245 (96.8%)	237 (96.7%)	977 (98.0%)
Subjects Did Not Complete Treatment Phase as Scheduled (Screening – Day 35)	50 (20.3%)	47 (18.6%)	43 (17.0%)	50 (20.4%)	190 (19.1%)
Adverse event	4 (1.6%)	1 (0.4%)	2 (0.8%)	4 (1.6%)	11 (1.1%)
Selection criteria/compliance	32 (13.0%)	33 (13.0%)	31 (12.3%)	33 (13.5%)	129 (12.9%)
Lost to follow-up	9 (3.7%)	10 (4.0%)	7 (2.8%)	10 (4.1%)	36 (3.6%)
Subject request	5 (2.0%)	3 (1.2%)	2 (0.8%)	2 (0.8%)	12 (1.2%)
Other	0	0	1 (0.4%)	1 (0.4%)	2 (0.2%)
Subjects Completed Treatment Phase as Scheduled (Screening – Day 35)	196 (79.7%)	206 (81.4%)	210 (83.0%)	195 (79.6%)	807 (80.9%)
Subjects with Interventions (Day 0 – Day 35)[c]	4 (1.6%)	9 (3.6%)	4 (1.6%)	4 (1.6%)	21 (2.1%)
Blood transfusion	1 (0.4%)	4 (1.6%)	2 (0.8%)	2 (0.8%)	9 (0.9%)
IV iron outside of protocol	1 (0.4%)	2 (0.8%)	0	1 (0.4%)	4 (0.4%)
Oral iron outside of protocol	2 (0.8%)	3 (1.2%)	2 (0.8%)	1 (0.4%)	8 (0.8%)
Subjects Did Not Complete Study as Scheduled (Screening – Day 120)	46 (18.7%)	49 (19.4%)	61 (24.1%)	58 (23.7%)	214 (21.5%)
Adverse event	2 (0.8%)	3 (1.2%)	4 (1.6%)	4 (1.6%)	13 (1.3%)
Study compliance	26 (10.6%)	24 (9.5%)	35 (13.8%)	35 (14.3%)	120 (12.0%)
Lost to follow-up	12 (4.9%)	18 (7.1%)	14 (5.5%)	15 (6.1%)	59 (5.9%)
Subject request	4 (1.6%)	4 (1.6%)	3 (1.2%)	1 (0.4%)	12 (1.2%)
Physician decision	1 (0.4%)	0	0	0	1 (0.1%)
Other	1 (0.4%)	0	5 (2.0%)	3 (1.2%)	9 (0.9%)
Subjects Completed Study as Scheduled (Screening – Day 120)	200 (81.3%)	204 (80.6%)	192 (75.9%)	187 (76.3%)	783 (78.5%)

Note: Percentages are based on the Safety Population.
Note: Sample sizes for subjects randomized were based on planned treatment. All other sample sizes were based on actual treatment.
a Total = number randomized/number not randomized.
b All subjects in the Safety Population who had at least 1 post-baseline hemoglobin assessment.
c Subjects could have had multiple interventions.

From sponsor's table in study report for 1VIT09031

Efficacy Results: The sponsor's analysis of the primary efficacy endpoint evaluated mean change from baseline to the highest observed hemoglobin any time between baseline and end of treatment period (Day 35) or time of intervention for the mITT population (all patients who received a dose of randomized treatment and had at least 1 post baseline hemoglobin assessment). The analysis showed that the difference between randomized treatment groups for both Cohorts 1 and 2 was significantly greater with FCM treatment than with the comparator. Results of the statistical analyses of the primary efficacy endpoint were

confirmed by FDA Statistical Review (KY Lee, Ph.D., 6/28/2012) as shown in the following two tables:

Table 12: Mean Change in Hemoglobin from Baseline to the Highest Value between Baseline and Day 35 (or time of intervention) (mITT) (Cohort 1 in Study 1VIT9031)

	FCM (N=244)	Oral Iron (N=251)
N	244	251
Baseline		
Mean (SD)	10.59 (1.01)	10.62 (1.03)
Highest		
Mean (SD)	12.16 (1.11)	11.42 (1.18)
Change		
Adjusted Mean*	1.52	0.76
Adjusted Difference (95% CI)*	0.76 (0.59, 0.93)	
p-value *	<0.0001	

*:ANCOVA with treatment and etiology of IDA as fixed factors and baseline hemoglobin as a covariate.

FDA Statistical Review (KY Lee, 6/28/2012)

Table 13: Mean Change in Hemoglobin from Baseline to the Highest Value between Baseline and Day 35 (or time of intervention) (mITT) (Cohort 2 in Study 1VIT9031)

	FCM (N=245)	IV SC (N=237)
Baseline		
Mean (SD)	9.12 (1.60)	9.02 (1.47)
Highest		
Mean (SD)	12.02 (1.22)	11.17 (1.26)
Change		
Adjusted Mean*	2.93	2.12
Adjusted Difference (95% CI)*	0.81 (0.61, 1.00)	
p-value *	<0.0001	

*:ANCOVA with treatment and etiology of IDA as fixed factors and baseline hemoglobin as a covariate.

FDA Statistical Review (KY Lee, 6/28/2012)

Supportive secondary efficacy analyses showed the results included the following table. These secondary efficacy analyses supported the findings of the primary analysis.

Study 1VIT09031: Secondary Efficacy Analyses (mITT Population)

	Cohort 1			Cohort 2		
	FCM (N=244)	Oral Iron (N=251)	p-value	FCM (N=245)	Oral Iron (N=251)	p-value
Proportion of subjects with Hgb>12 g/dL[a], n (%)	139 (57.0%)	73 (29.1%)	<0.0001	124 (50.6%)	58 (24.5%)	<0.0001
Mean change in ferritin from baseline to highest value[a] [adjusted mean]	532.34	3.55	<0.0001	518.03	130.82	<0.0001
Proportion of subjects with Hgb>12 g/dL and an increase in ferritin	133 (54.5%)	1 (0.4%)	<0.0001	118 (48.2%)	14[b] (5.9%)	<0.0001

≥160 ng/mL[a], n (%)						
Proportion of subjects with clinically meaningful increase in Hgb[ac], n (%)	80 (32.8%)	22 (8.8%)	<0.0001	164 (66.9%)	113[b] (47.7%)	<0.0001

[a]anytime between baseline and Day 35 (or time of intervention)
[b] N=237 [c] defined as ≥1 g/dL in hemoglobin for CKD, ≥2 g/dL for HUB or GI disorders, ≥3 g/dL for postpartum and ≥2 g/dL for others

from tables in FDA Statistical Review by KY Lee (6/28/2012)

Findings for mean increase in hemoglobin, ferritin, TSAT serum iron and mean decrease in TIBC and unsaturated IBC were consistent with the efficacy findings of the primary analysis. For both Cohorts the efficacy findings were similar across range of baseline hemoglobin values and across various etiologies of iron deficiency anemia. See FDA Statistical Review by KY Lee (6/28/2012) for more detail.

The sponsor's analysis for the mean change in hemoglobin for the various iron deficiency anemia sub-populations in the study are shown in the table below.

Study 1VIT09031: Summary of Mean Change in Hemoglobin from Baseline to the Highest Value Between Baseline and Day 35 or Time of Intervention for Iron Deficiency Anemia Populations (mITT Population)

	Cohort 1		Cohort 2	
	Group A: FCM (N=244)	Group B: Oral Iron (N=251)	Group C: FCM (N=245)	Group D: IV SC (N=237)
Etiology of IDA HUB				
Baseline				
n	125	123	108	106
Mean (SD)	10.67 (1.092)	10.57 (1.000)	9.14 (1.889)	9.00 (1.644)
Highest Value				
n	125	123	108	106
Mean (SD)	12.27 (1.079)	11.51 (1.225)	12.16 (1.184)	10.99 (1.360)
Change to Highest Value				
n	125	123	108	106
Mean (SD)	1.60 (1.257)	0.94 (0.823)	3.02 (1.599)	1.99 (1.308)
Etiology of IDA GI Disorders				
Baseline				
n	26	27	57	53
Mean (SD)	10.22 (0.855)	10.41 (0.937)	9.28 (1.329)	9.34 (1.270)
Highest Value				
n	26	27	57	53
Mean (SD)	11.98 (1.351)	10.95 (1.008)	11.99 (1.294)	11.30 (1.150)
Change to Highest Value				
n	26	27	57	53
Mean (SD)	1.76 (1.102)	0.54 (0.578)	2.71 (1.481)	1.96 (1.120)
Etiology of IDA Other				
Baseline				
n	93	101	80	78
Mean (SD)	10.60 (0.912)	10.74 (1.091)	8.98 (1.328)	8.83 (1.300)
Highest Value				
n	93	101	80	78
Mean (SD)	12.07 (1.082)	11.43 (1.151)	11.85 (1.213)	11.34 (1.155)
Change to Highest Value				
n	93	101	80	78
Mean (SD)	1.48 (1.136)	0.68 (0.791)	2.87 (1.802)	2.52 (1.193)

SD=standard deviation

From sponsor's table in the 1VIT09031 study report

Safety Results: The safety population consisted of all patients who received a dose of randomized treatment. In the safety population during the treatment phase all patients randomized to FCM (both cohorts) received the total prescribed dose (median dose, 1500 mg; mean dose, 1435 mg). In the IV standard of care (IV SC) arm, 230 patients (93.9%) received up to 5 doses of IV iron (median dose, 800 mg; mean dose, 813 mg). Median maximum single injection was 750 mg for the FCM arms (mean, 733 mg) and 200 mg for the IV SC arm (mean, 309 mg). During the Follow-up phase (Days 35 through 120) a small number of patients (14 in the FCM arms, 7 in the oral iron arm, and 19 in the IV SC arm received additional iron). For subjects randomized to IV SC, the majority of patients received Venofer (iron sucrose) (220/245; 89.8%) and 23 (9.4%) received iron dextran. Among patients randomized to oral iron the median total dose received was 2730 mg (mean 2608 mg) with a median exposure of 14 days (mean, 13.9 days).

To evaluate the cardiovascular safety of FCM during the study a composite safety endpoint was specified, consisting of: all cause mortality, myocardial infarction, stroke, unstable angina requiring hospitalization, congestive heart failure requiring hospitalization or intervention, arrhythmia, hypertensive events, and hypotensive events. Criteria for these events were specified in the protocol and a blinded Clinical Events Committee adjudicated all suspected clinical endpoint events. The sponsor's analysis of the composite safety endpoint is shown in the summary table below.

Study 1VIT09031: Summary of Primary Composite Safety Endpoint (Safety Population)

	Cohort 1		Cohort 2	
	Group A: FCM (N=246) n/N (%)	Group B: Oral Iron (N=253) n/N (%)	Group C: FCM (N=253) n/N (%)	Group D: IV SC (N=245) n/N (%)
All Subjects	7/246 (2.85%)	4/253 (1.58%)	10/253 (3.95%)	12/245 (4.90%)
Baseline Hemoglobin				
≤9.0 g/dL	2/23 (8.70%)	0/24	4/122 (3.28%)	6/120 (5.00%)
9.1-10.0 g/dL	1/48 (2.08%)	3/48 (6.25%)	3/60 (5.00%)	6/60 (10.00%)
≥10.1 g/dL	4/175 (2.29%)	1/181 (0.55%)	3/71 (4.23%)	0/65
Baseline Cardiovascular Risk Category				
0-1	5/191 (2.62%)	0/185	5/200 (2.50%)	6/188 (3.19%)
2-3	2/55 (3.64%)	4/68 (5.88%)	5/53 (9.43%)	6/57 (10.53%)
Etiology of IDA				
HUB	4/126 (3.17%)	0/124	3/111 (2.70%)	3/109 (2.75%)
GI disorders	0/26	1/27 (3.70%)	2/59 (3.39%)	5/56 (8.93%)
Other	3/94 (3.19%)	3/102 (2.94%)	5/83 (6.02%)	4/80 (5.00%)

Note: One Group B (oral iron) subject (310132) had a hypotension event during the oral iron Run-In Phase that is not reflected in this table.

From sponsor's table in the 1VIT09031 study report

The cardiovascular analysis showed similar results for the FCM and IV SC treatments for Cohort 2. For Cohort 1 the number of events was smaller for the oral iron arm. However, in the study rates of these adverse events were low. Most of the adjudicated events were hypertension events or hypotension events. Events comprising the cardiovascular safety endpoint are summarized in the following table.

Study 1VIT09031: Summary of Components of the Primary Composite Safety Endpoint (Safety Population)

	Cohort 1		Cohort 2	
	Group A: FCM (N=246)	Group B: Oral Iron (N=253)	Group C: FCM (N=253)	Group D: IV SC (N=245)
Any	7 (2.85%)	4 (1.58%)	10 (3.95%)	12 (4.90%)
Components of Composite Endpoint[a]				
Death due to any cause	0	2 (0.79%)	1 (0.40%)	1 (0.41%)
Nonfatal myocardial infarction	0	0	1 (0.40%)	0
Nonfatal stroke	0	1 (0.40%)	0	0
Unstable angina requiring hospitalization	0	1 (0.40%)	0	0
Congestive heart failure	0	0	0	0
Arrhythmias	0	1 (0.40%)	0	0
Protocol-defined hypertensive events	4 (1.63%)	0	7 (2.77%)	6 (2.45%)
Protocol-defined hypotensive events	3 (1.22%)	1 (0.40%)	1 (0.40%)	5 (2.04%)
Composite Endpoint Excluding Protocol-Defined Hypertensive and Hypotensive Events	0	4 (1.58%)	2 (0.79%)	1 (0.41%)
Death, Myocardial Infarction, or Stroke	0	3 (1.19%)	2 (0.79%)	1 (0.41%)

Note: One Group B (oral iron) subject (310132) had a hypotension event during the oral iron Run-In Phase that is not reflected in this table.

From sponsor's table in the 1VIT09031 study report

Causes of deaths occurring in this study were: 2 in Oral iron arm (1 septic shock; 1 death not otherwise specified after study exit); 1 in FCM arm in Cohort 2 (malignant lung neoplasm); 1 in IV SC in Cohort 2 (accidental overdose per autopsy report)

See Dr. Lu's Clinical Review (signed in DARRTS 6/8/2012) for more detailed description of the safety results.

Study 1Vit09030 (REPAIR-IDA):

Study 1VIT09030 was a multicenter, randomized, open-label, active controlled study comparing safety and efficacy of ferric carboxymaltose to iron sucrose (Venofer) in adult patients with iron deficiency anemia and impaired renal function (non-dialysis dependent). The study was conducted from 9/4/2009 to 6/15/2011 in 187 sites in the U.S. Important inclusion criteria included (1)hemoglobin $\leq$11.5 g/dL and (2)either: GFR <60 mL/min/1.73 m^2 (on 2 screening measurements) or GFR <90 mL/min/1.73 m^2 (on 2 screening measurements) and evidence of kidney damage or elevated risk of cardiovascular disease (Framingham Category 2 or 3). Patients requiring dialysis for chronic kidney disease or being considered for initiation of hemodialysis during the time period of the trial were not enrolled, On screening patients must have serum ferritin $\leq$100ng/mL or $\leq$300 ng/mL when transferrin saturation (TSAT) is $\leq$30%. ESA use was allowed provided patients were on stable dose at study entry. Exclusion criteria were essentially the same as for Study 1VIT09031, except that patients having or requiring a surgical procedure that necessitates general anesthesia (other than vascular access surgery) were excluded. The primary objective of the study was to estimate the cardiovascular safety and the efficacy of FCM compared to intravenous iron sucrose in subjects with iron deficiency anemia and impaired renal function. The primary endpoint was a composite cardiovascular safety endpoint consisting of: death due to any cause, nonfatal myocardial infarction, nonfatal stroke, unstable angina requiring hospitalization, congestive heart failure requiring hospitalization or medical intervention, arrhythmias, hypertension, and

hypotension. The target sample size of 1250 patients was estimated to provide >95% power to demonstrate noninferiority with a 95% 2-sided confidence interval and a noninferiority margin of 0.2 g/dL for the difference between FCM and Venofer in the mean increase from baseline to the highest observed hemoglobin any time between baseline and end of treatment period (Day 56) or time of intervention. The primary analysis population was a modified intent to treat (mITT) population defined as all randomized patients receiving at least one dose of randomized study drug, having at least one post-baseline hemoglobin assessment and having a stable ESA dose (or 0 dose) for 4 weeks before randomization.

Patients were randomized (1:1) to ferric carboxymaltose (FCM) 15mg/kg to a maximum of 750 mg per dose administered on Days 0 and 7 (total maximum cumulative dose of 1500 mg) as an undiluted IV push injection at 100 mg/min or to Venofer 200 mg on day 0, 7 and 14 with two additional doses given: one between days 0 and 7 and the other between days 7 and 14. ESA dose could be decreased or stopped during the study but not increased or restarted. Randomization was stratified by baseline cardiovascular risk, country/region, ESA use, and CKD stage.

After receiving first randomized treatment dose (Day 0) Patients were to be seen on Days 3 ($\pm$2), 7, 11 ($\pm$2), 14 and 28 and Day 56 for follow-up. There was an additional telephone follow-up contact on Day 90 and a final clinic visit on Day 120.

Study 1VIT09030 was conducted from September 4, 2009 through June 15, 2011 at 187 U.S. centers.

Demographics and Disposition: A total of 2584 patients were randomized (1290 to FCM; 1294 to Venofer). Of these, 14 randomized to FCM and 9 randomized to Venofer discontinued prior to dosing, mainly due to subject request or selection criteria/study compliance reasons.

Demographics and important baseline characteristics for the 2561 patients who were randomized and received study drug are shown in the following table:

Study 1VIT09030: Demographics and Important Baseline Characteristics

Baseline Characteristic	FCM N=1276	Venofer (N=1285)	Total (N=2561)
Age (years)\			
Mean (SD)	67.5 (13.00)	67.2 (13.00)	67.3 (12.99)
Median	69	69	69
$\leq$65	500 (39.2%)	536 (41.7%)	1036 (40.5%)
Gender			
Female	810 (63.5%)	818 (63.7%)	1628 (63.6%)
Male	466 (36.5%)	467 (36.3%)	933 (36.4%)
Race			
African American	334 (26.2%)	325 (25.3%)	659 (25.7%)
Asian	20 (1.6%)	21 (1.6%)	41 (1.6%)
Caucasian	676 (53.0%)	693 (53.9%)	1369 (53.5%)
Hispanic	234 (18.3%)	236 (18.4%)	470 (18.4%)
Other	12 (0.9%)	10 (0.8%)	22 (0.9%)
Weight (kg)			

n	1275	1285	2560
Mean (SD)	89.65 (24.747	165.70 (24.770)	89.68 (24.754
Median	85.3	86.6	86.2
BMI (kg/m^2)			
n	1273	1285	2558
Mean (SD)	32.60 (8.677)	32.65 (8.614)	32.63 (8.644)
Median	31.0	31.4	31.2
CKD Stage			
2	68 (5.3%)	78 (6.1%)	146 (5.7%)
3-4	1113 (87.2%)	1105 (86.0%)	2218 (86.6%)
5	95 (7.4%)	102 (7.9%)	197 (7.7%)
Baseline GFR-MDRD			
Mean (SD)	32.50 (14.722)	32.27 (14.900)	32.38 (14.809)
Median	31	30	30
Minimum, Maximum	5, 91	6, 90	5, 91
Baseline hemoglobin, g/dL			
Mean (SD)	10.31 (0.833)	10.32 (0.826)	10.31 (0.830)
Median	10.5	10.5	10.5
Minimum, maximum	6.4, 11.8	5.4, 11.6	5.4, 11.8
Baseline TSAT (%)			
Mean (SD)	19.79 (7.777)	19.56 (7.397)	19.68 (7.588)
Median	20	20	20
Minimum, maximum	3, 55	3, 63	3, 63
<20%	660 (51.7%)	662 (51.5%)	1322 (51.6%)
Baseline Ferritin (ng/mL)			
Mean (SD)	73.01 (64.624)	75.05 (64.116)	74.03 (64.365)
Median	54.2	57.0	55.7
Minimum, maximum	2.1, 606.0	2.1, 599.5	2.1, 606.0
<100 ng/mL	955 (74.8%)	943 (73.4%)	1898 (74.1%)
ESA Use			
No	1046 (82.0%)	1057 (82.3%)	2103 (82.1%)
Yes	230 (18.0%)	228 (17.7%)	458 (17.9%)
History of:			
Previous iron therapy	696 (54.5%)	693 (53.9%)	1389 (54.2%)
Iron intolerance	67 (5.3%)	63 (4.9%)	130 (5.1%)
Drug allergy	571 (44.7%)	587 (45.7%)	1158 (45.2%)
Myocardial infarction	197 (15.4%)	184 (14.3%)	381 (14.9%)
Stroke	165 (12.9%)	157 (12.2%)	322 (12.6%)
Congestive heart failure	315 (24.7%)	309 (24.0%)	624 (24.4%)

SD=standard deviation; CKD=chronic kidney disease; GFR=glomerular filtration rate: BMI=body mass index; MDRD=modification of diet in renal disease

Reviewer's table based on data from sponsor's tables in study report for 1VIT09030

Treatment groups were well-balanced for the baseline demographic and other characteristics. Mean age was about 67 years and about 63% of patients were female. Baseline hemoglobin was 10.5 g/dL, about 82% of patients were receiving an ESA and transferring saturation was <20% in about 51% of patients. About 54% of patients had received previous iron therapy. Approximately 15% had history of myocardial infarction, 13% history of stroke, and 24% history of congestive heart failure.

The disposition of enrolled patients is summarized in the sponsor's table below.

Study 1VIT09030: Disposition of Subjects (all Randomized)

	Group A: FCM	Group B: Venofer	Total
Subjects Randomized	1290	1294	2584
Subjects Treated (Safety Population)	1276	1285	2561
mITT Population[a]	1249 (97.9%)	1244 (96.8%)	2493 (97.3%)
Subjects Did Not Complete Treatment Phase as Scheduled (Screening – Day 56)	228 (17.9%)	243 (18.9%)	471 (18.4%)
Adverse event	20 (1.6%)	22 (1.7%)	42 (1.6%)
Selection criteria/compliance	181 (14.2%)	188 (14.6%)	369 (14.4%)
Lost to follow-up	11 (0.9%)	10 (0.8%)	21 (0.8%)
Subject request	9 (0.7%)	17 (1.3%)	26 (1.0%)
Physician decision	3 (0.2%)	2 (0.2%)	5 (0.2%)
Other	4 (0.3%)	4 (0.3%)	8 (0.3%)
Subjects Completed Treatment Phase as Scheduled (Screening – Day 56)	1048 (82.1%)	1042 (81.1%)	2090 (81.6%)
Subject Had an Intervention[b]	100 (7.8%)	96 (7.5%)	196 (7.7%)
Increased dose of EPO (Day 0 – Day 56)	71 (5.6%)	60 (4.7%)	131 (5.1%)
Blood transfusion	15 (1.2%)	22 (1.7%)	37 (1.4%)
IV iron outside of protocol	4 (0.3%)	5 (0.4%)	9 (0.4%)
Oral iron outside of protocol	10 (0.8%)	17 (1.3%)	27 (1.1%)
Start dialysis	15 (1.2%)	4 (0.3%)	19 (0.7%)
Subjects Did Not Complete Study as Scheduled (Screening – Day 120)	217 (17.0%)	212 (16.5%)	429 (16.8%)
Adverse event	35 (2.7%)	30 (2.3%)	65 (2.5%)
Study compliance	138 (10.8%)	131 (10.2%)	269 (10.5%)
Lost to follow-up	23 (1.8%)	23 (1.8%)	46 (1.8%)
Subject request	17 (1.3%)	22 (1.7%)	39 (1.5%)
Physician decision	2 (0.2%)	1 (0.1%)	3 (0.1%)
Other	2 (0.2%)	5 (0.4%)	7 (0.3%)
Subjects Completed Study as Scheduled (Screening – Day 120)	1059 (83.0%)	1073 (83.5%)	2132 (83.2%)
Time in Study (days)			
≥7	1271 (99.6%)	1275 (99.2%)	2546 (99.4%)
≥14	1261 (98.8%)	1268 (98.7%)	2529 (98.8%)
≥21	1258 (98.6%)	1263 (98.3%)	2521 (98.4%(
≥28	1258 (98.6%)	1257 (97.8%)	2515 (98.2%)
≥56	1245 (97.6%)	1245 (96.9%)	2490 (97.2%)
≥84	1226 (96.1%)	1229 (95.6%)	2455 (95.9%)
≥119	1207 (94.6%)	1209 (94.1%)	2416 (94.3%)

Note: Percentages are based on the Safety Population.

a All subjects in the Safety Population who had at least 1 post-baseline hemoglobin assessment and had stable (within 20%) EPO dosing for 4 weeks, which may have included a dose of 0, before randomization.

b Subjects could have had multiple interventions.

From sponsor's table in study report for 1VIT09031

Approximately 18% of patients discontinued study treatment prematurely (mainly due to selection criteria/compliance) and approximately 82% of patients completed study treatment as planned. Premature discontinuations were slightly more common in the FCM arm (mainly due to study compliance) (17.0% and 16.5% in the FCM and Venofer arms, respectively) as were interventions of increased ESA dose and Start dialysis (increased ESA: 5.6% and 4.7% in the

FCM and Venofer arms, respectively; start dialysis: 1.2% and 0.3% in the FCM and Venofer arms, respectively).

Efficacy Results: The sponsor's analysis of the primary efficacy endpoint evaluated mean change from baseline to the highest observed hemoglobin any time between baseline and end of treatment period (Day 56) or time of intervention for the mITT population (all patients who received a dose of randomized treatment and had at least 1 post baseline hemoglobin assessment). The primary efficacy analysis is shown in the following table from the FDA Statistical Review (KY Lee, Ph.D., 6/28/2012).

Table 6 : Mean Change in Hemoglobin from Baseline to the Highest Value between Baseline and Day 56 (or time of intervention): mITT Population (Study 1VIT9030)

	FCM (N=1249)	Venofer (N=1244)
Baseline		
Mean (SD)	10.31 (0.83)	10.33 (0.83)
Highest		
Mean (SD)	11.44 (1.19)	11.25 (1.08)
Change		
Mean (SD)	1.13 (1.04)	0.92 (0.92)
Difference (95% CI)	0.21 (0.13, 0.28)	

FDA Statistical Review (KY Lee, 6/28/2012)

The Statistical Review found that FCM was statistically non-inferior to Venofer for the mean change in hemoglobin for the mean change in hemoglobin to the highest value between baseline and Day 56 or time of intervention (lower limit (0.13) of the 95% CI above the noninferiority margin of -0.2 g/dL). The efficacy results were reasonably consistent with and without concomitant ESA use and across range of baseline hemoglobin values and CKD stages. See Dr. Lu's Clinical Review for presentations of subset and other supporting analyses.

Safety Results: The safety population consisted of all patients who received at least one dose of randomized treatment. The maximum single injection was 750 mg iron for FCM and 200 mg iron for Venofer. In the FCM arm 96.8% of patients received two injections and the median cumulative dose was 1500 mg iron (mean 1464 mg) and in the Venofer arm 91.6% of patients received 5 injections with a median cumulative dose of 1000 mg iron (mean 962.9 mg).

Cardiovascular safety was assessed using the same composite safety endpoint as used in Study 1VIT09031, which consisted of: all cause mortality, myocardial infarction, stroke, unstable angina requiring hospitalization, congestive heart failure requiring hospitalization or intervention, arrhythmia, hypertensive events, and hypotensive events.

Table 15. Summary of the Primary Composite Safety Endpoint (Safety Population)

Subject Group	Group A: FCM (N=1276) n/N (%)	Group B: Venofer (N=1285) n/N (%)	Difference (95% CI)[a]
Overall	175/1276 (13.71%)	156/1285 (12.14%)	1.57% (-1.10%, 4.25%)
Baseline Hemoglobin			
≤9.0 g/dL	15/103 (14.56%)	13/102 (12.75%)	1.82% (-8.55%, 12.19%)
9.1-10.0 g/dL	51/286 (17.83%)	31/292 (10.62%)	7.22% (1.20%, 13.23%)
≥10.1 g/dL	109/887 (12.29%)	112/891 (12.57%)	-0.28% (-3.46%, 2.90%)
EPO Use			
No	146/1046 (13.96%)	132/1057 (12.49%)	1.47% (-1.52%, 4.46%)
Yes	29/230 (12.61%)	24/228 (10.53%)	2.08% (-4.21%, 8.37%)
CKD Stage			
2	4/68 (5.88%)	3/78 (3.85%)	2.04% (-6.37%, 10.45%)
3-4	149/1113 (13.39%)	141/1105 (12.76%)	0.63% (-2.27%, 3.52%)
5	22/95 (23.16%)	12/102 (11.76%)	11.39% (-0.16%, 22.95%)

CI=confidence interval
a CI constructed with the normal approximation to the binomial with Wald continuity correction.

From sponsor's table in the 1VIT09030 study report

Rates of the composite endpoint tended to be higher in the FCM group as compared to the Venofer group for most comparisons; however, the differences between the treatment groups were not statistically significant.

Table 16. Summary of the Components of the Primary Composite Safety Endpoint (Safety Population)

Composite Safety Endpoint	Group A: FCM (N=1276) n (%)	Group B: Venofer (N=1285) n (%)	Difference (95% CI)[a]
Any	175 (13.71%)	156 (12.14%)	1.57% (-1.10%, 4.25%)
Components of the composite endpoint[b]			
Death due to any cause	15 (1.18%)	18 (1.40%)	-0.23% (-1.18%, 0.73%)
Nonfatal myocardial infarction	8 (0.63%)	14 (1.09%)	-0.46% (-1.25%, 0.33%)
Nonfatal stroke	3 (0.24%)	3 (0.23%)	0.00% (-0.45%, 0.45%)
Unstable angina requiring hospitalization	11 (0.86%)	3 (0.23%)	0.63% (-0.02%, 1.28%)
Congestive heart failure requiring hospitalization or medical intervention	38 (2.98%)	34 (2.65%)	0.33% (-1.03%, 1.69%)
Arrhythmias	18 (1.41%)	13 (1.01%)	0.40% (-0.53%, 1.32%)
Protocol-defined hypertensive events	95 (7.45%)	56 (4.36%)	3.09% (1.19%, 4.99%)
Protocol-defined hypotensive events	23 (1.80%)	41 (3.19%)	-1.39% (-2.67%, -0.10%)
Composite endpoint excluding protocol-defined hypertensive and hypotensive events	70 (5.49%)	69 (5.37%)	0.12% (-1.72%, 1.95%)
Death, myocardial infarction, or stroke	24 (1.88%)	35 (2.72%)	-0.84% (-2.08%, 0.40%)

CI=confidence interval
a CI constructed with the normal approximation to the binomial with Wald continuity correction.
b Subjects may have experienced more than 1 component of the composite safety endpoint.

From sponsor's table in the 1VIT09030 study report

Examination of the components of the composite cardiovascular endpoint found the overall numerical difference between treatments disfavoring FCM to be due mainly to protocol-defined hypertensive events (FCM, 7.45%; Venofer, 4.36%). Death due to any cause was slightly less for FCM (1.18%) than for Venofer (1.40%).

See Dr. Lu's Clinical Review (signed in DARRTS 6/8/2012) for more detailed description of the safety results.

Other Clinical Information:
Overall Safety: The sponsor has conducted 26 clinical studies of FCM involving 6679 subjects exposed to FCM. FCM has been marketed abroad since 2007. For the pooled five studies where the maximum 750 mg single dose of FCM was used, mortality rates were 0.7% (17/2566) for FCM-treated patients and 0.8% (22/2590) for comparator-treated patients. For all completed studies, the overall mortality rate was 0.5% (33/6679) in the FCM-treated patients and 0.6% (30/5394) in the comparator-treated patients. See the safety assessment and risk benefit assessment sections in the Clinical Review by M. Lu, M.D. (signed in DARRTS 6/8/2012) for more detailed description of the safety findings.

Pediatrics: No pediatric patients were studied for the current NDA. To address PREA (Pediatric Research Equity Act) the sponsor proposes a waiver for patients less than (b) (4) years of age and proposes studies in patients (b) (4) years (b) (4).

The sponsor has requested a waiver for conducting pediatric studies in patients less than (b) (4) years of age, "due to logistical challenges associated with subjects of this age range" and citing previous pediatric experience with its other intravenous iron product, Venofer (iron sucrose), recruiting patients from birth to <2 years of age into Phase III trials.

> [Note: Pediatric studies of Venofer for iron deficiency anemia in patients age <2 years with non-dialysis dependent chronic kidney disease (CKD) receiving or not receiving an erythropoietin were waived (NDA 21-135 letter dated June 17, 2005) (too few children with disease to study). With the original approval of Venofer for iron deficiency anemia in patients with hemodialysis-dependent chronic kidney disease, pediatric studies of Venofer in neonates and infants were not required, however, a post-marketing commitment (PMC) #1 requested additional information for possible need for and risks involved with Venofer® use in very young pediatric patients (approval letter dated November 6, 2000). A letter was sent to the sponsor on December 6, 2001 that PMC #1 had been fulfilled].

For older pediatric patients ((b) (4) to 17 years) the sponsor proposes two trials: (1)a pharmacokinetic/pharmacodynamic (PK/PD) study to characterize the PK of serum iron and determine appropriate dosing of FCM for the pediatric population with iron deficiency anemia and (2)a safety and efficacy trial of FCM versus iron sucrose. The sponsor proposes to submit the full protocol(s) for the studies within one year of NDA approval, begin recruitment within 18 months after NDA approval and submit the final study report by the end of 2016.

Comments and Recommendations:
In this NDA the sponsor has provided two randomized, controlled studies that demonstrate efficacy and adequate safety of Injectafer (ferric carboxymaltose, FCM) given at a total dose of 1500 mg iron administered as two intravenous doses of 750 mg each separated by 7 days for treatment of iron deficiency in the populations studied. Study 1VIT09030 evaluated use of FCM in patients with non-dialysis dependent chronic kidney disease and iron deficiency anemia. In this study FCM was found to be noninferior to labeled use of Venofer (iron sucrose) for increasing hemoglobin in these patients. Study 1VIT09031 evaluated use of FCM in a population of patients with iron deficiency anemia due a variety of causes (heavy uterine bleeding in about half of patients) who were intolerant of or had unsatisfactory response to oral

iron. In this study FCM administered as two intravenous doses of 750 mg each separated by 7 days was found to be superior to oral iron (ferrous sulfate 325 mg orally three times daily for 14 days) in increasing hemoglobin.

With regard to safety, analysis of the two studies did not reveal evidence of a safety disadvantage for FCM as compared to the active control for the composite cardiovascular safety endpoint. The evaluation of mortality for the proposed labeling dose used in the two pivotal studies and for single dose administration of FCM 750 mg iron in the overall clinical study database showed similar rates for FCM as compared to the active comparator.

Overall, from a clinical viewpoint, the benefit-risk assessment for Injectafer with dosing of 15 mg/kg up to a maximum single dose of 750 mg of iron on two occasions separated by at least 7 days up to a cumulative dose of 1500 mg of iron delivered by intravenous infusion or injection appears acceptable for treatment of iron deficiency anemia in the studied populations. The wording of the indication in the labeling should reflect the populations studied.

The labeling for Injectafer should carry all the Warnings and Precautions as the currently approved parenteral iron products.

There are no recommendations from clinical for post-marketing studies. A waiver for pediatric studies required under PREA for the indication should be granted for studies of Injectafer in patients less than (b) (4) years of age, because of too few children with the disease to study. Pediatric studies in older children may be deferred; however, protocols for proposed studies should be submitted for review.

Reviews and recommendations from other disciplines should be considered for decision on regulatory action.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATHY M ROBIE SUH
07/20/2012

DIVISION OF HEMATOLOGY PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA:	203565/SD20
Drug names:	Injectafer
Indications:	Treatment of Iron Deficiency Anemia
Route of administration:	IV
Sponsor:	Luitpold Pharmaceuticals Inc
Submission:	Resubmission; Safety Update
Date submitted:	January 30, 2013; March 13, 2013; March 20, 2013
Review completed:	June 25, 2013
Medical Reviewer:	Min Lu, M. D., M. P. H

Background and Rationale

The NDA 203565 Injectafer was submitted on September 30, 2011 and a Complete Response (CR) was issued on July 23, 2012 due to deficiencies found in the inspection of the manufacturing facility.

On January 30, 2013, the sponsor submitted the response to the Agency's CR letter with an alternative manufacture site for Injectafer. The CMC information is currently under review by FDA ONDQA. The sponsor has also submitted two safety reports for Injectafer based on post-marketing experiences from outside of U.S. as requested by the Division. The following is the summary of the submitted safety information.

Safety Update

The sponsor submitted a periodic safety update report covering 18 June 2011-17 June 2012 and a bridge safety report covering 18 June 2012 - 31 January 2013 from Vifor Pharma as safety update for this resubmission.

Ferinject (name of product in other countries sponsored by Vifor Pharm) was first approved on 6 July 2007 in the Netherlands and first launched in the EU in Germany in November 2007. The marketing authorization in the EU was renewed in 2012. To date, Ferinject has received regulatory approval for marketing authorization in 45 countries

worldwide. During the reporting period Ferinject gained regulatory approval in Israel, Italy, Singapore, New Zealand, Peru, Turkey, Brazil, Iran, Croatia and Pakistan.

During the reporting period covered by this PSUR, there have been changes to the reference safety information (RSI). The following changes to the RSI have been implemented during the reporting period:

- Deletion of the contraindication pregnancy in the first trimester following the request of some EU health authorities
- Addition of hypertension as a new adverse drug reaction (ADR) due to pooled analysis of clinical data
- Changes in ADR frequencies due to availability of new clinical trial data
- Introduction of a post-marketing section listing undesirable effects from post-marketing spontaneous reporting (hypersensitivity-related symptoms)

Market Experience

The total number of patients exposed to the product was calculated from the number of ampoules sold, assuming that 1 patient requires (b) (4) ampoules of Ferinject containing 100 mg iron each, or (b) (4) ampoules of Ferinject containing 500 mg iron each per year. The estimate of (b) (4) mg iron ((b) (4) ampoules of 100 mg iron or (b) (4) ampoules of 500 mg iron) per year is considered as an average requirement.

The estimated exposure was 197,291 patient-years in the period from 18 June 2011-17 June 2012 and 194,300 patient years in the period from 18 June 2012 to 31 January 2013. The cumulative estimated exposure since the international birth date is 677,168 patient years.

Case Reports

During the period from 18 June 2011-17 June 2012, 700 cases (spontaneous, literature, clinical trial and other) associated with a total of 1,442 AEs were reported. These included 149 serious cases and 551 non-serious cases. A total of 9 fatal cases were received during the reporting period. Five cases were from clinical trials and the other 4 cases were spontaneous reports. One case of bronchospasm followed by cardiorespiratory arrest was assessed as related to Ferinject and one case of embolic stroke (6 hours after Ferinject administration with atrial fibrillation) was assessed by the reporter as possibly related. The other seven reports were assessed as unrelated (lung neoplasm, myocardial infarction [3 cases], respiratory infection, and cardiac failure [2 cases]).

During the period from 18 June 2012 to 31 January 2013, 544 cases with a total of 1,150 AEs (from spontaneous, literature, clinical trials and other) were identified. These included 108 serious cases and 436 non-serious cases. A total of 6 fatal cases were received during the reporting period. Two cases were from clinical trials and the other 4 cases were spontaneous reports. These included two fetal deaths. One case of anaphylactic shock was assessed as related to Ferinject and all other reports were

assessed as unrelated (chronic heart failure, cervical spine fracture, aspiration pneumonia and respiratory failure, cerebral hemorrhage).

For both reporting periods, the most frequently reported adverse drug reactions (ADRs) were General Disorders and Administration Site Conditions, Skin and Subcutaneous Disorders, and Injury Poisoning and Procedural Complications. The following two tables summarize the reported AEs by system organ class (SOC) for each reporting period.

In the period from 18 June 2011-17 June 2012

Table 1 **Summary Tabulation of Adverse Events by MedDRA SOC (All Related Spontaneous, Clinical Trial, Literature and Other Solicited Cases)**

SOC	Serious AEs		Non-serious AEs		Total
	Listed	Unlisted	Listed	Unlisted	
Blood and Lymphatic System Disorders	–	1	–	–	1
Cardiac Disorders	2	4	6	4	16
Ear and Labyrinth Disorders	1	2	9	2	14
Eye Disorders	–	1	1	7	9
Gastrointestinal Disorders	21	6	75	6	108
General Disorders and Administration Site Conditions	64	7	321	28	420
Hepatobiliary Disorders	–	3	–	–	3
Immune System Disorders	48	–	22	–	70
Infections and Infestations	–	4	1	3	8
Injury, Poisoning and Procedural Complications	5	3	148	2	156
Investigations	13	11	11	9	44
Metabolism and Nutrition Disorders	1	3	2	5	11
Musculoskeletal and Connective Tissue Disorders	8	3	28	7	39
Nervous System Disorders	20	10	64	12	105
Pregnancy, Puerperium and Perinatal Conditions	–	3	–	–	3
Psychiatric Disorders	–	–	3	10	13
Renal and Urinary Disorders	–	2	–	1	3
Reproductive System and Breast Disorders	–	–	–	4	4
Respiratory, Thoracic and Mediastinal Disorders	10	5	19	12	46
Skin and Subcutaneous Disorders	58	8	228	14	308
Social Circumstances	–	–	–	2	2
Surgical and Medical Procedures	–	–	1	4	5
Vascular Disorders	12	4	20	9	45
Total	**262**	**80**	**959**	**141**	**1442**

Notes: AE = Adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SOC = System organ class.

In the period from 18 June 2012 to 31 January 2013

Table 1 Summary Tabulation of ADRs by MedDRA SOC (Spontaneous, Literature and Related Solicited Cases) in Period June 2012 to January 2013

SOC	Serious ADRs		Non-serious ADRs		Total
	Listed	Unlisted	Listed	Unlisted	
Infections and Infestations	–	1	1	4	6
Blood and Lymphatic Disorders	–	2	–	–	2
Immune System Disorders	31	1	23	–	55
Metabolism and Nutrition Disorders	3	2	4	2	11
Psychiatric Disorders	–	6	1	2	9
Nervous System Disorders	15	8	38	5	66
Eye Disorders	–	1	1	1	3
Ear and Labyrinth Disorders	–	1	1	3	5
Cardiac Disorders	2	10	2	3	17
Vascular Disorders	11	6	10	3	30
Respiratory, Thoracic and Mediastinal Disorders	11	8	10	8	37
Gastrointestinal Disorders	16	1	47	9	73
Skin and Subcutaneous Disorders	44	4	134	20	202
Musculoskeletal and Connective Tissue Disorders	10	2	27	6	45
Renal and Urinary Disorders	–	1	–	1	2
Pregnancy, Puerperium, and Perinatal Conditions	–	6	–	–	6
Reproductive System and Breast Disorders	–	–	–	8	8
Congenital, Familial and Genetic Disorders	–	1	–	–	1
General Disorders and Administration Site Conditions	27	5	287	24	343
Investigations	4	2	6	12	24
Injury Poisoning and Procedural Complications	17	–	181	2	200
Surgical and Medical Procedures	1	–	3	–	4
Social Circumstances	–	1	–	–	1
Total	**192**	**69**	**776**	**113**	**1,150**

Notes: ADR = Adverse drug reaction; MedDRA = Medical Dictionary for Regulatory Activities; SOC = System organ class.

In the period from 18 June 2011 to 17 June 2011, there were 255 serious listed ADRs in 126 cases and 79 serious unlisted ADRs in 51 cases. In the period from 18 June 2012 to 31 January 2013, there were 192 serious listed ADRs in 91 cases and 69 serious unlisted ADRs in 48 cases.

The most reported serious listed ADRs (≥3 cases) included hypersensitivity, dyspnea, type I hypersensitivities, urticaria, anaphylactic reactions, anaphylactoid reactions/shock, hypotension, rash, pruritus, overdose, chest pain, angioedema, erythema, arthralgia, pyrexia, chills, malaise, nausea, headache, dizziness, syncope, abdominal pain, blood pressure decreased, blood pressure increased, skin discoloration, extravasation, injection side pain, face edema, back pain, myalgia, and hypophosphatemia.

The most reported serious unlisted ADRs (≥2 cases) included circulatory collapse, cyanosis, shock, asthenia, C-reactive protein increased, fetal death, bradycardia, agitation,

throat irritation, hyperhidrosis, and phlebitis. The events of circulatory collapse, cyanosis, bradycardia, agitation, and throat irritation are also associated with other hypersensitivity reactions. These cases are considered as hypersensitivity cases. Asthenia is closely related to fatigue (listed).

Pregnancy-related Case Reports

In the period from 18 June 2011 to 17 June 2012, one fetal death and one case of pre-syncope during pregnancy were described in the safety report.

In the period from 18 June 2012 to 31 January 2013, 48 cases of drug exposure during pregnancy were received. During this reporting period, there were 6 serious unlisted pregnancy-related cases and 2 fetal death cases.

Three additional fetal deaths were recently reported through IND 63243.

The following table summarizes the reported seven cases of pregnancy-related serious unlisted adverse events:

Cases of Pregnancy-related Serious Unlisted Adverse Events

Cases	Mother (age, pregnancy)	Ferinject Exposure	Time to Event	Events	Pregnancy Outcome
VIT-2012-00927	26 years, 36 weeks	100 mg	immediately	Mother: Presyncope, nausea, dizziness, pallor. Resolved.	Normal
VIT-2012-02305	28 years 3rd trimester (unspecified date)	200 mg	25 days	Mother: Hemolysis, Cardiovascular disorder, LDH increase, Fatigue, Headache. Ongoing.	Unknown
VIT-2012-03980	Unknown age, 30 weeks	100 mg	5 minutes	Mother: Dyspnea, Pallor. Resolved. Fetus: Bradycardia	Normal
VIT-2012-04347	Unknown age, Diabetic, 15 and 19 weeks	500 mg 2 doses,	?21-25 weeks	Fetus: Caudal regression syndrome, Premature baby	Premature baby with Caudal regression syndrome.
VIT-2013-00055:	31 years, 39 weeks	500 mg	immediately	Vertigo, Blood pressure decreased	Normal
VIT-2012-02358:	Unknown age, unknown week	Unknown dose	immediately	Paralysis	Unknown
VIT-2012-03537:	39 years, 29 weeks	500 mg	2 minutes	Mother: malaise and position dependent	Normal

				retrosternal pain, Pulmonary embolism	

The following table summarizes the six cases of fetal deaths:

Cases of Fetal Deaths

Cases	Mother	Ferinject Exposure	Time to Event	Events
Reported in Safety Updates				
VIT-2011-01294:	40 years, History of spontaneous miscarriages, 31 weeks	500 mg, 2 doses, 23 weeks	2 months	Fetal death
VIT-2012-04145	Unknown age, 34 weeks	100 mg, 34 weeks	1 day	Fetal death due to "heart disorder"
VIT-2012-04167	Unknown age, Positive anti-S antibodies and cold antibodies, 39 weeks	1000 mg, in 37 weeks	2 weeks	Fetal death
Reported through IND				
1256-214 Received on 2/27/13 by FDA	40 years, 30 weeks	Unknown dose, 2 doses, in week 10	2 months	Fetal death
1256-232 Received on 5/6/13 by FDA	20 years, History of Henoch-Schonlein purpura, 39 weeks	1000 mg, 2 doses, 38 weeks	1 week	Lack of fetal movement, fetal death
1256-240 Received on 6/12/13 by FDA	30 years, diabetes gravidarum, 39 weeks	1000 mg 36 weeks	2 hours	Lack of fetal movement, fetal death

The narratives of these cases are presented below.

Serious unlisted related pregnancy cases:

Mfr. Control Number VIT-2012-00927: Presyncope, nausea, dizziness, pallor, maternal exposure during pregnancy
This medically confirmed case concerns a 26-year-old female patient with a medical history of antibiotic allergy (drug name was not provided). The patient had experienced similar AEs in the past to other unspecified drug. The patient was pregnant at the time of

the report, gestational period 36 weeks and 1 day. The patient was administered 100 mg of IV iron as Ferinject in an unspecified dilution, over an unspecified period of time, for anemia (drug exposure during pregnancy). After administration of Ferinject the patient experienced dizziness, nausea, a pale complexion and pre-syncope. After discontinuation of Ferinject administration, the patient recovered from the events. She was re-administered the remaining Ferinject mixed with normal saline 50 cc. After administration of the remaining Ferinject the patient did not experience any AEs. On an unspecified date the patient delivered a normal baby girl. The reporter considered the events nausea, dizziness, paleness and pre-syncope to be related to Ferinject. The causality assessment for the event drug exposure during pregnancy with Ferinject was not applicable.

Mfr. Control Number VIT-2012-02305: Hemolysis, Cardiovascular disorder, blood lactate dehydrogenase (LDH) increase, Fatigue, Headache, Maternal exposure during pregnancy

This case was in a 28-year-old pregnant female patient (third trimester of pregnancy), with a medical history of gestational diabetes and surgery, who was treated with IV iron as iron carboxymaltose (Ferinject), with a dose of 200 mg, diluted in 100 mL of NaCl, given over an unknown period of time. About 25 days later, the patient experienced hemolysis, isolated LDH increase, headache, exhaustion and circulatory problems. The patient did not receive any treatment medication. The patient received erythrocyte concentrates. The patient had not recovered from the events at the time of the report. The reporter assessed the causality for the events hemolysis, isolated LDH increase, headache, exhaustion and circulatory problems with Ferinject as related.
The sponsor considered that time to onset between Ferinject administration and the events reported makes a relationship improbable, but not impossible. The case is not assessable due to the lack of detailed information.

Mfr. Control Number VIT-2012-03980: Bradycardia fetal, Dyspnea, Pallor, Maternal exposure during pregnancy

This case concerns a 30-week pregnant female patient of unknown age, with an unspecified medical history and concomitant medication use. The patient was treated with IV iron as iron carboxymaltose (Ferinject), with a dose of 100 mg, diluted in 50 mL of normal saline solution and given over an unknown period of time for anemia. Five minutes after administration, the patient experienced dyspnea and became pale. Fetal bradycardia was detected for 6 minutes with fetal heart rate at 58 beats per minute (normal range 120-150). The patient recovered without sequelae from the events. On an unspecified date the patient gave birth to a healthy baby, with no other complications for both the mother and the baby. The reporter did not provide a causality assessment for the events dyspnea, pallor and fetal bradycardia with Ferinject. The sponsor assessed the events to be related to Ferinject.

Mfr. Control Number VIT-2012-04347: Caudal regression syndrome, Premature baby, Fetal exposure during pregnancy, Maternal exposure during pregnancy

This report was received from the French Health Authorities and concerns a 6-month-old female infant born premature with caudal regression syndrome. Maternal history included severe Type I diabetes since the age of 18 with multiple complications of nephropathy.

The mother of the patient experienced intrauterine growth retardation during her pregnancy. In the 15th and 19th week of pregnancy the mother of the patient was treated with IV iron carboxymaltose (Ferinject), at a dose of 500 mg in an unspecified dilution, given over an unspecified period of time. Concomitant medication included insulin glargine, darbepoetin alfa, midodrine hydrochloride, valsartan, fluoxetine, and folic acid. The patient's mother had a very poor diabetic balance with hemoglobin A1C of 12.32%. The infant was the first child. The patient had not recovered from the event of caudal regression syndrome. The therapies with Ferinject, darbepoetin alfa, midodrine hydrochloride, valsartan, fluoxetine and folic acid were discontinued. The reporter did not provide a causality assessment for the events caudal regression syndrome and prematurity with Ferinject. The sponsor considered that the events reported are possibly but unlikely related to Ferinject because the administration of Ferinject was after the period of organogenesis finished and there are several high risk factors in the mother such as diabetes mellitus Type I and the nephropathy.

Mfr. Control Number VIT-2013-00055: Vertigo, Blood pressure decreased, Maternal exposure during pregnancy

This case concerns a 31-year-old pregnant (Week 39) woman. The patient had 2 pregnancies before, a spontaneous birth in 2007 and a caesarean birth in 2009, without any complications. During a past pregnancy the patient received iron sucrose (Venofer®) for IDA in pregnancy and showed a hypotonic reaction. The patient was administered as premedication 2 ampoules of butylscopolamine (Buscopan) diluted in 1,000 mL NaCl during 6 hours until 1 hour prior to IV iron carboxymaltose (Ferinject) administration with a dose of 500 mg, diluted in 100 mL NaCl, over 5 minutes, for IDA. The infusion was administered on the dorsal left lower arm using a venflon access. During the Ferinject administration, the patient felt slightly vertiginous. The patients' blood pressure dropped from 120/80 mmHg to 80/29 mmHg and then 73/36 mmHg. A pathological cardiotocography (CTG) was observed, which showed severe, variable deceleration. The infusion was immediately stopped. The patient received IV ephedrine treatment. Within 30 minutes, the patient fully recovered from the events. The patient gave birth to a healthy female baby 5 days after treatment (APGAR score 8-8-9). The baby's weight was 2,790 g and height was 47 cm. The reporter considered the events slight vertigo and drop in blood pressure to be related to Ferinject.

Mfr. Control Number VIT-2012-02358: Paralysis, Maternal exposure during pregnancy

This case concerns a pregnant female patient of unspecified age who was treated with IV iron carboxymaltose (Ferinject) with an unknown dose for an unspecified indication at home by a nurse on an unspecified date. Right after the beginning of the infusion, the patient experienced body blockage, the patient could not move her body or breathe. The cause of the event was not found. No treatment was given. The patient recovered from the events within an unspecified period of time. The patient refused to continue her treatment with Ferinject. The patient delivered a few days later without any problems and was lost to follow-up for any further details. The reporter did not provide causality assessment for the events and Ferinject.

Mfr. Control Number VIT-2012-03537: Pulmonary embolism, Maternal exposure during pregnancy

The reported case concerns a 39-year-old pregnant female patient (29th gestational week) who was taking ethinylestradiol before pregnancy for contraception and was concomitantly taking Rajopton® (herbal extract and Omega 3 and ergocalciferol) and was treated with IV iron carboxymaltose (Ferinject), at a dose of 500 mg, diluted in 100 mL NaCl, given over a period of 15 minutes for IDA. This was the first time the patient received Ferinject. Two minutes after the Ferinject infusion, the patient experienced malaise and position dependent retrosternal pain. The patient was hospitalized at the emergency department where a pulmonary embolism was diagnosed, based on the patient's symptoms, the complete blood tests done and the positive D-dimer test. The therapy with Ferinject was discontinued. The patient remained for (b) (6) in the hospital and was treated with enoxaparin sodium. Complete blood test results were not provided. No CT scan or X-ray or any other investigation was performed. The patient recovered completely from the events of malaise, position dependent retrosternal pain and pulmonary embolism (b) (6) later. The outcome of the pregnancy was normal. The reporter assessed the causality for the events with Ferinject as related. The sponsor considered that the event could be related to ethinylestradiol use and being pregnant.

Fetal death cases:

Mfr. Control Number VIT-2011-01294: Fetal death, maternal exposure during pregnancy

This case concerns a 40-year-old pregnant female patient with a medical history of 3 spontaneous miscarriages before 8 weeks of pregnancy, one in 2009, one in 2010 and one in 2011. The patient was treated with IV iron as Ferinject 500 mg twice for anemia. Eight months after conception and 2 months after Ferinject exposure, the patient lost cervical plug after intercourse resulting in a male fetus weighing 1.05 kg expelled at 31 weeks and 5 days. Fetal death was diagnosed the same day, however examination revealed macerated fetus without any external or visceral malformation, the development corresponded to a 27 to 28 weeks. Serology for paravirus infection showed: B19 immunoglobulin G (IgG) -8.02 (N<1.5, positive test), serology for Epstein-Barr virus infection showed: IgG anti-viral capsid antigen antibody >750 UA/mL (N<20, positive test), IgG anti Epstein-Barr virus nuclear antigen antibody -157 UA/mL (positive test), toxoplasmosis test revealed IgG 24.2 UL/mL (>10.5 positive test) (only abnormal test results are shown). It was unknown if the patient was exposed to toxin. The reporter did not provide a causality assessment for fetal death, macerated fetus and drug exposure during pregnancy with Ferinject.

Mfr. Control Number VIT-2012-04145: Fetal death

The case concerns a fetus in the 34th week of gestation; the mother of the fetus (age unknown) was treated with IV iron carboxymaltose (Ferinject) with a dose of 100 mg, for an unspecified indication. The following day, the fetus died due to a heart disorder. The mother was hospitalized for further care. The patient had discontinued Ferinject on an unspecified date. No further information was provided. The reporter considered the event

"fetal death" to be not related to Ferinject. The sponsor agrees with the assessment of the reporter. The same case is also reported as VIT-2012-04144 (mother case).

Mfr. Control Number VIT-2012-04167: Fetal death, Fetal exposure during pregnancy

This case concerns a fetus of unknown gender whose mother had anti-S antibodies and cold antibodies who was transplacentally exposed to carboxymaltose (Ferinject), at a dose of 1,000 mg given to the mother 13 days before the delivery due date. During the first trimester of the pregnancy, the mother of the fetus experienced blood loss and fever of unknown origin. An ultrasound showed a low implanted placenta which could have been the cause of the blood loss. A Combi-test showed no trisomy 18, 13 or 21 in the fetus. A standard ultrasound at 20 weeks of gestation showed that the fetus was a little bit small for gestational age (from the beginning of pregnancy onward) and, the placenta was in a higher position in comparison with the prior ultrasound examination. During the whole pregnancy the mother felt baby movements. At 25.5 weeks of pregnancy the mother came to hospital because of less baby movements, however CTG showed no abnormalities and ultrasound showed the growth of baby according to gestational age. At 35.5 weeks of pregnancy hemoglobin was 10.5 g/dL. When the mother was 37 weeks and 4 days pregnant the mother received Ferinject. The next day the patient felt less fetal movements. The patient went for a check-up to the hospital and underwent a CTG which was good and no abnormalities were found on examination. Nine days later the patient could clearly feel good baby movements; however the next day at 39.5 weeks of pregnancy, the patient again felt less fetal movement and underwent a second CTG. The CTG showed that the fetus had died. The magnetic resonance imaging of the fetus was unremarkable. The pathological assessment of the placenta was unremarkable. The umbilical cord showed more than normal squiggles, a feature associated with intrauterine fetal death. The reporter provided a causality assessment for the event fetal death with Ferinject as not related as the most likely cause of the event was due to anti-S antibodies. The sponsor agrees with the reporter's assessment.

Three additional fetal deaths were recently reported through IND 63243.

Case 1 (Mfr Report #1256-214):

On 22-Feb-2013, the sponsor received this report from Vifor International Inc. This initial report concerns a 40-year old pregnant female patient with no significant co-morbidities. The patient was not on other drug therapies. The patient's last menstruation period (LMP) was on 16-Nov-2011. In a regular cycle of 28 days, the date of conception was 30-Nov-2011. On 20-Dec-2011 and on 10-Jan-2012 (week 10 of pregnancy), during her pregnancy, the patient was treated with iron carboxymaltose (Ferinject), two times in total, at an unspecified dose, in an unspecified dilution, given over an unspecified period of time, for an unspecified indication. According to the Ferinject SmPC of Switzerland, it is contraindicated to use Ferinject during the first trimester of the pregnancy. Fetal death occurred in utero. The patient underwent curettage in (b) (6). The action taken with Ferinject therapy was not reported. The reporter considered the events drug exposure during pregnancy and fetal death in utero to be possibly related to Ferinject.

Case 2 (Mfr Report 1256-232):
On 29-Apr-2013, the sponsor received this report from Vifor International Inc. This initial report was received from a physician in Finland. This report concerns a baby, born on (b) (6). The mother was a 20-year old female with a medical history of Henoch-Schonlein purpura in 2011, migraine and had no symptoms of Henoch-Schonlein after the 1st trimester. The mother developed iron deficiency anemia during her pregnancy. The paternal grandmother had congenital heart disease. The mother was concomitantly taking ferrous glycine sulphate (Obsidan) and Lactoferrin for iron deficiency. On 18-Mar-2013 and 25-Mar-2013, during 38th+4 week of pregnancy, the mother was treated with iron carboxymaltose (Ferinject) at two doses of 1000 mg in an unknown dilution and given over an unknown period of time for iron deficiency anemia. After the first administration of Ferinject, the mother experienced malaise and dizziness, but hemoglobin modestly increased. She received the second Ferinject injection and red blood cell transfusions and felt better. The last time the fetus moved "correctly" was 0 1-(b) (6), the mother came to the hospital because of lack of fetal movement. She was diagnosed with suspected partial placental ablation. The mother was sent urgently to the delivery ward. The mother had contractions earlier (time unspecified), but these had subsided. A cardiotocography (CTG) was performed which showed a curve which denoted bradycardia. An ultrasonic scan also confirmed bradycardia and narrow uterus. An emergency caesarean was performed. The amniotic fluid contained blood. The baby was lifeless and was admitted to the intensive care unit for revitalization; however, died on the same day. The placenta was disconnected from the uterine cavity. At the edge of ablation, significant sickle shaped change was observed. Partial ablation of the placenta was suspected. Therapy with Ferinject was discontinued. The reporter did not provide the causality assessment for the events placenta ablation, death neonatal, and bradycardia with Ferinject.

Case 3 (safety report SD#361 faxed 6/6/13):
On June 03, 2013, the sponsor received a spontaneous report of a fetal death from Vifor International (2013-00605). This initial spontaneous report was received by Vifor from a Health Authority (NL-LRB-154571) in Netherlands and concerns a fetus with drug exposure in utero. The mother of the fetus was a 30-year-old pregnant female patient with a medical history of postnatal depression after 2 previous pregnancies and diabetes gravidarum. The mother was concomitantly taking sertraline hydrochloride (Sertraline) since 2009 for an unknown indication. The lab data of the mother included hemoglobin 5.2 mmol/L (normal reference range was not provided). The mother's diabetes gravidarum was controlled with diet and glucose level was regulated well. The mother had no known past drug therapy. On (b) (6), the mother was treated with intravenous iron carboxymaltose (Ferinject) at a dose of 1000 mg, in an unspecified dilution, given over an unspecified period of time, for anemia. The mother received Ferinject at 36+6 weeks of her pregnancy. On (b) (6), 2 hours after the end of Ferinject administration, the mother did not feel fetal movements anymore and 12 hours later intrauterine death was diagnosed. It was reported that the mother's condition of diabetes gravidarum and possible interference with other drugs could have contributed to the event. The mother did not experience any adverse event. The action taken with Ferinject therapy was reported as not applicable. This case was serious (death, important

medical event). The reporter did not assess the causality for the event intrauterine death with Ferinject.

Case reports of hypophosphatemic rickets and osteomalacia

The following post-marketing case was reported through IND reports.

On 31-Jan-2012, Vifor received the initial report from a health authority via a company representative in Norway and subsequent information from the literature article Falck Moore KL, Kildahl-Andersen O, Kildahl-Andersen R, Tjonnfjord GE; "Uncommon adverse effect of a common medication"; Tidsskr Nor Legeforen 2013 JAN 01; 133; 165 (see attached). The report concerns a 55-year-old female with a medical history of suffering for many years (since 1996), from iron deficiency anemia as a result of "unexplained heavy urinary iron loss". She had been receiving blood transfusions and intravenous iron supplements for 15 years, most recently in the form of large doses of iron (III) carboxymaltose. Concomitant medication included paracetamol (Paracet), metoprolol (Selo-Zok), ibuprofen (Ibux), and loratidine (Claritiyn). In Sep-2010, the patient was started on treatment with intravenous iron as iron carboxymaltose (Ferinject) at a dose of 500-1000 mg, in an unspecified dilution, given every 2-3 weeks for iron deficiency. The patient received in total 6 injections over 9 months (up to 9-Jun-2011). On an unspecified date in Feb-2011, the patient had gradually developed pain extending from the lower back to both gluteal regions. Blood tests in Jun-2011 revealed normal calcium, low phosphate and elevated alkaline phosphatase levels, parathyroid hormone in the upper normal range, and normal 25-OH vitamin D and 1,25-(OH)2 vitamin D values. Magnetic resonance imaging (MRI) in Jun-2011 detected high signal changes in both sacral wings and later also on the ileal side, indicating substantial bone edema. There were radiolucent lines in the sacral wings which raised suspicion of bilateral insufficiency fractures. Full body scintigraphy showed increased uptake in the anterior section of the frontal bone on both sides of the midline, in several ribs, both sacroiliac joints, and proximally in the left tibia. The verbatim reported by the Norwegian Health Authority was hypophosphatemic osteomalacia, which they coded to two preferred terms (MedDRA coded: Hypophosphataemic rickets/unexpected and Osteomalacia/ unexpected). Therapy with Ferinject was discontinued in Jun-2011. At a check-up five months after termination of all iron supplements, the patient was recovering. MRI showed regression of pathological changes. However, the patient still needs treatment for iron deficiency anemia and is now receiving a different type of iron supplement intravenously. Her need for transfusion varies somewhat, depending on how often she receives iron. This case was assessed as serious (important medical event, permanent disability, and hospitalization). The Norwegian Health Authority assessed the causal relationship between Ferinject and hypophosphatemic osteomalacia as possible.

Case reports for overdose and medication error

The following overdose case was reported in the Safety update during this report period.

Mfr. Control Number VIT-2013-00046, Arthropathy, Walking disability, Iron overload, Asthenia, Haemosiderosis, Drug Prescribing error, Drug dispensing error

This case was reported by the French Health Authority (ANSM, 98-2013) and concerns a 40-year-old female patient with a medical history of obesity with bypass, intolerance to oral iron and ID. The patient was concomitantly taking Vitamin B12 for Vitamin B12 deficiency. The patient took ferrous sulphate (Tardyferon) in the past, which proved ineffective. For 5 months the patient was treated with IV iron as iron carboxymaltose (Ferinject), at an unspecified dose, in an unknown dilution over an unknown period of time for anemia related to iron despoliation due to bypass. The patient received 18 infusions in total, 3 infusions per month for 6 months. Ferinject was administered as an IV infusion at home. The physician used to prescribe 2 infusions of Ferinject 1,000 mg however the physician prescribed 3 infusions of Ferinject 1,000 mg, denoting a prescription error. On the same prescription, the physician also prescribed Vitamin B12, to be renewed 6 times (i.e., once per month for 6 months). The pharmacist made a delivery error as the pharmacist understood that Ferinject was also to be renewed 6 times. As a consequence, the patient received 18,000 mg of Ferinject within 6 months. The physician stated that the prescribed Ferinject injection was without renewal. The event reported was misinterpretation of prescription by the pharmacist. Iron overload was noted with ferritin >4,000 mg/L and transferrin saturation around 92%. At the time of the report, the patient experienced joints disorder, hemosiderosis, metallic complexion and asthenia. The patient was in a wheelchair. The events were still ongoing, lasting for over 4 months. The patient received an iron chelator (deferasirox (Exjade®)) 1,250 mg per day) and blood-letting for 6 months (10 blood-lettings in total at the time of the report) as remedial therapy. On an unspecified date, the patient started walking again. The patient recovered from the event of "could not walk anymore". The clinical condition was slowly improving however the patient was still disabled in the patient's motor abilities. At the time of the report, the patient was recovering from the events joints disorder, hemosiderosis, metallic complexion and asthenia. The reporter assessed the events reported with Ferinject as related. According to the reporter, the events were related to Ferinject, however not strictly related to the drug but rather to a wrong prescription.

Conclusions and Recommendations

In the reporting period from June 18, 2011- January 31, 2013, there were seven serious pregnancy-related cases reported in the safety reports and four of them were likely to be related to hypersensitivity reactions in mothers. Fetal bradycardia or abnormal cardiotocography was observed in two cases. Healthy baby or normal pregnancy was reported in four cases and no outcomes of fetus were reported in 2 cases. One case reported fetal Caudal regression syndrome in a diabetic mother who received iron carboxymaltose 500mg for two doses during the 2nd trimester.

Three fetal deaths were reported in the safety updates and 3 additional fetal deaths were recently reported through IND reports. Exposure to iron carboxymaltose occurred during the 1st trimester in one case, the 2nd trimester in one case, and in 3rd trimester for 4 cases. The fetal deaths occurred between 12 hours and 2 months after the last dose of iron carboxymaltose. In three of five cases, the mother had significant underlying medical conditions or history of spontaneous miscarriages. No detailed information was available in two cases.

This reviewer has the following recommendation:

1. Consult PHMS for fetal death cases and pregnancy-related cases of serious adverse events for further evaluation.
2. Describe the post-marketing hyperphosphatemic osteomalacia case and include adverse reactions that have not been identified from the clinical trials in Section 6.2. Adverse Reactions from Post-marketing Spontaneous Reports of the label.
3. Describe the post-marketing cases of iron overdose and hyperphosphatemic osteomalacia and in Section 10. Overdosage of the label.

See my previous review (dated 6/8/2012) for other labeling recommendations.

From clinical perspective, this application should be approved with revised labeling.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MIN LU
07/09/2013

KATHY M ROBIE SUH
07/09/2013
Final wording of the labeling is being developed with the review team and will be negotiated with the sponsor.

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	203565/000
Priority or Standard	Standard
Submit Date(s)	September 30, 2011
Received Date(s)	October 3, 2011
PDUFA Goal Date	August 3, 2012
Division / Office	DHP/OHOP
Reviewer Name(s)	Min Lu, M.D., M.P.H.
Review Completion Date	May 22, 2012
Established Name	Ferric Carboxymaltose
(Proposed) Trade Name	Injectafer
Therapeutic Class	Intravenous Iron Injection
Applicant	Luitpold Pharmaceuticals, Inc.
Formulation(s)	100 mg of elemental iron/ (b) (6) vials
Dosing Regimen	15 mg/kg; Maximum single dose of 750 mg; Maximum cumulative dose of 1500 mg
Indication(s)	Treatment of iron deficiency anemia
Intended Population(s)	Patients with iron deficiency anemia

Table of Contents

Table of Tables

Table of Figures

Abbreviations

ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CEC	Clinical Events Classification
CFR	Code of Federal Regulations
CHF	Congestive Heart Disease
CI	Confidence Interval
CKD	Chronic Kidney Disease
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Event
dL	Deciliter
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EPO	Erythropoietin
ESA	Erythropoiesis-Stimulating Agent
FCM	Ferric Carboxymaltose (VIT-45)
FDA	Food and Drug Administration
Fe	Iron
g	Gram
GFR	Glomerular Filtration rate
GGT	Gamma Glutamyl Transferase
GI	Gastrointestinal
Hb (Hgb)	Hemoglobin
HDD-CKD	Hemodialysis Dependent Chronic Kidney Disease
HUB	Heavy Uterine Bleeding
IBC	Iron Binding Capacity
IBD	Inflammatory Bowel Disease
ICH	International Corrference on Harmonization
IDA	Iron Deficiency Anemia
IND	Investigational Drug Application
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
IV SD	Intravenous Iron Standard Care
kg	Kilogram
LDH	Lactic Dehydrogenase
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
mITT	Modified Intent-to-Treat
mg	Milligram

mL	Milliliter
rnrnHg	Millimeters Mercury
NCI	National Cancer Institute
NDA	New Drug Application
NDD-CKD	Non-dialysis dependent chronic kidney disease
ng	Nanogram
PCS	Potentially Clinically Significant
PO	Orally
PD	Pharmacodynamics
PK	Phamacokinetics
PMC	Postmarket Commitment
PREA	Pediatric Research Equity Act
RBC	Red Blood Cell
RDW	Red Cell Distribution Width
RES	Reticulo-Endothelial System
sc	Standard of Care
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
TID	Three Times Daily
TSAT	Transferrin Saturation
ULN	Upper Limit of Normal
U.S.	United States
WBC	White Blood Cell

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, Injectafer should be approved for the indication for the treatment of iron deficiency anemia in patients who are intolerant to oral iron or have had unsatisfactory response to oral iron and in patients with non-dialysis dependent chronic kidney disease.

1.2 Risk Benefit Assessment

Two randomized controlled pivotal trials (1VIT09031 and 1VIT09030) were conducted to support the efficacy of Injectafer with the proposed dose regimen of 15 mg/kg with the maximum individual dose of 750 mg and a total dose of 1,500 mg. Study 1VIT09031 was conducted in patients with iron deficiency anemia who had an inadequate response to oral iron treatment, who were intolerant to oral iron during the 14-day run-in period, or who were deemed unsuitable by the Investigator for the oral iron, mainly due to low hemoglobin level with or without co-morbidities. Study 1VIT09030 was conducted in patients with non-dialysis dependent chronic kidney disease (NDD-CKD). Both clinical studies were randomized, open-label, controlled studies. In Study 1VIT09031, oral iron was used as control in patients who had an inadequate response to oral iron treatment in Cohort 1 and other IV iron products (mostly Venofer) were used as control in patients who were intolerant to oral iron in Cohort 2. In Study 1VIT09030, Venofer was used as control in patients with NDD-CKD. The primary efficacy endpoint was the mean change from baseline to the highest observed hemoglobin observed anytime between baseline and Day 35 or time of intervention in Study 1VIT09031 and between baseline and Day 56 or time of intervention in Study 1VIT09030.

In Study 1VIT09031, the results show that the mean increase in hemoglobin from baseline to the highest value between baseline and Day 35 or time of intervention in the Injectafer group was statistically significantly greater than that in the oral iron group in Cohort 1 (1.57 g/dL vs. 0.80 g/dL, $p<0.01$) and also higher than that in the IV standard care group (2.90 g/dL vs. 2.16 g/dL, $p<0.01$) in Cohort 2. In Study 1VIT09031, the mean increase in hemoglobin from baseline to the highest value between baseline and Day 56 or time of intervention in the Injectafer group was non-inferior to Venofer (1.13 g/dL vs. 0.92 g/dL, treatment difference 0.21 g/dL [95% CI 0.13-0.28 g/dL]). The results from the secondary efficacy endpoints analyses including hemoglobin response and iron indices were consistent with the primary efficacy analysis results in both studies. The results from subgroup analyses including baseline hemoglobin level and etiology of iron deficiency anemia in Study 1VIT09031 and baseline hemoglobin, EPO use and CKD stage in Study 1VIT09030 were all consistent with the results from the primary efficacy endpoint analyses.

A total of 1775 subjects have received the proposed Injectafer dosing regimen of 15mg/kg with the maximum of single dose of 750 mg and maximum total dose of 1500 mg in two pivotal clinical studies. The majority of patients have received 750 mg dose for 2 doses. A total of 2566

subjects have been exposed to Injectafer as a maximum single dose of 750 mg with the different total doses. A total of 6679 subjects have been exposed to Injectafer with different dosing regimens in the Phase 2/3 development program.

The mortality rates were similar between Injectafer for the proposed dosing regimen and the comparators in pooled analysis of the two pivotal studies (16/1775, 0.9% vs. 21/1783, 1.2%) and were also similar between Injectafer with the maximum single dose of 750 mg with the different total doses and the comparator in pooled analysis of the five clinical studies (17/2566, 0.7% vs. 22/2590, 0.8%). For all completed studies, the overall mortality rate was 0.5% (33/6679) in the Injectafer-treated patients and 0.6% (30/5394) in comparator-treated patients.

In the two pivotal trials, no significant difference was found for the pre-specified primary cardiovascular composite safety endpoint (including death, MI, stroke, unstable angina, CHF, hypertension and hypotension) between Injectafer and Venofer or pooled comparators (10.8%, 11.1%, and 9.7%, respectively). Hypertensive events were found to be significantly higher in the Injectafer group as compared to the Venofer group, or the pooled comparator group (6.0%, 4.1%, and 3.5%, respectively).

In the two pivotal trials, the overall incidence of treatment-emergent serious adverse events was 12.8% in the Injectafer group, 14.0% in the Venofer group, and 12.5% in the pooled comparators group. The most common treatment-emergent serious adverse events in the Injectafer group were cardiac failure congestive (1.7%) and pneumonia (1.0%), which were similar to values in the pooled comparators and Venofer groups. The incidence of treatment-emergent adverse events resulting in premature discontinuation of study drug was 2.9% in the Injectafer group, 2.3% in the Venofer group, and 2.1% in the pooled comparators group. The most common treatment-emergent adverse events resulting in premature discontinuation of study drug in the Injectafer group were flushing and hypertension (0.5% and 0.6%, respectively).

The incidence of treatment-emergent serious or severe hypersensitivity/allergic reactions was 1.5% in the Injectafer group, 1.6% in the Venofer group, and 1.5% in the pooled comparators group in the two pivotal trials.

In the two clinical trials, 60.3% of subjects in the FCM group experienced at least one treatment-emergent adverse event as compared to 59.0% of subjects in the Venofer group, and 55.2% of subjects in the pooled comparator group. The most common ($\geq$2.0%) treatment-emergent adverse events in the FCM group were nausea (11.4%), hypertension (8.6%), dizziness (4.3%), flushing (3.4%), headache (3.3%), vomiting (3.3%), diarrhea (3.2%), urinary tract infection (3.2%), hypotension (2.8%), hypophosphatemia (2.7%), constipation (2.3%), fatigue (2.3%), back pain (2.3%), peripheral edema (2.3%), and congestive heart failure (2.1%). Adverse events that occurred more frequently (by $\geq$1%) with Injectafer than with pooled comparator were nausea, hypertension, flushing, vomiting, hypophosphatemia, back pain, hyperkalemia, ALT increased, injection site discoloration, and hot flush.

The incidence of any drug-related treatment-emergent adverse event was greater in the FCM group (23.5%) compared with the Venofer (17.3%) and pooled comparators (15.9%) group. The most common (≥1.0%) drug-related treatment-emergent adverse events in the FCM group were nausea (7.2%), hypertension (3.8%), flushing (2.7%), hypophosphatemia (2.1%), dizziness (2.0%), vomiting (1.7%), injection site discoloration (1.4%), headache (1.2%), ALT increased (1.1%), and dysgesusia (1.1%). Drug-related treatment-emergent adverse events that occurred more frequently (by ≥1%) with Injectafer than with pooled comparator included nausea, hypertension, flushing, hypophosphatemia, vomiting, and injection site discoloration.

The overall benefit of Injectafer treatment is considered to outweigh the risk in the intended population.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The product labeling should include WARNINGS AND PRECAUTIONS for hypersensitivity, hypertension reactions and iron overload associated with Injectafer treatment. As for other intravenous iron products, the risk of hypersensitivity reactions under WARNINGS and PRECAUTIONS should be highlighted in bold letters.

1.4 Recommendations for Postmarket Requirements and Commitments

The applicant requested a deferral of pediatric studies in (b) (4) and 17 years of age group under PMRs and requested a waiver of a pediatric study in the 0-(b) (4) years of age group to meet the requirements of Pediatric Research Equity Act (PREA). The proposed pediatric studies in (b) (4) and 17 years of age group include one pharmacokinetic/pharmacodynamic study and one safety and efficacy study in pediatric patients with iron deficiency anemia. The applicant proposed to submit full pediatric study protocols within one year of approval and recruitment will begin within the first 18 months after the NDA is approved with the final study report being submitted on or before December 31, 2016. These requests should be granted.

2 Introduction and Regulatory Background

2.1 Product Information

Injectafer (ferric carboxymaltose injection, FCM) is a dark brown colloidal solution of polynuclear iron (III) hydroxide in complex. Each mL of Injectafer contains 50 mg iron as ferric carboxymaltose in water for injection. Injectafer is available in (b) (4) 15 mL single use vials. Sodium hydroxide and/or hydrochloric acid may have been added to adjust the pH.

Drug established name: ferric carboxymaltose injection
Proposed trade name: Injectafer
Chemical class: Intravenous iron products
Pharmaceutical class: Anti-anemia products
Proposed indication: Treatment of iron deficiency anemia.

2.2 Tables of Currently Available Treatments for Proposed Indications

Current available treatment for iron deficiency anemia includes oral iron products and intravenous iron products. The approved intravenous iron products in the U.S. include Iron dextran (INFeD and Dexferrum), Ferrlecit, Venofer, and Feraheme. Only iron dextrans have been approved for a broad population and others were approved for CKD population only. The approved indications, dose regimens and main safety concerns for these intravenous iron products are shown in the table below.

Table 1. Currently Approved Intravenous Iron Products in US

Chemical name	Iron Dextran (INFeD, Dexferrum)	Ferrlecit (Sodium Ferric gluconate complex)	Venofer (Iron Sucrose)	Feraheme (ferumoxytol)
Year of first U.S. approval	1974	1999 (marketed in Europe since 1950's)	2000 (marketed in Europe since 1950's)	2009
Indication	Treatment of patients with documented iron deficiency anemia in whom oral iron administration is unsatisfactory or impossible	Treatment of iron deficiency anemia in adult patients and in pediatric patients age 6 years and older with chronic kidney disease receiving hemodialysis who are receiving supplemental epoetin therapy	Treatment of iron deficiency anemia in adult patients with chronic kidney disease	Treatment of iron deficiency anemia in adult patients with chronic kidney disease
Safety	Box warning for anaphylactic-type reactions	Warning for hypersensitivity reactions	Warning for hypersensitivity reactions	Warning for hypersensitivity reactions
Population	Adults and Pediatrics	Adults and Pediatrics	Adults	Adults
Dose regimen	100 mg (2 mL) may be given on a daily basis until the calculated total amount required has been reached. It is given undiluted at a slow gradual rate not to exceed 50 mg per minute. Adults and Children over 15 kg (33 lbs): Total amount (mL) = 0.0442 (Desired Hb-Observed Hb) × LBW (kg) + (0.26 × LBW) Children 5-15 kg (11-	Adults: Total cumulative dose: 1,000 mg 125 mg for 8 doses at sequential dialysis session, by slow injection at a rate of up to 12.5 mg/min or infusion over 1 hour diluted in 100 mL of 0.9% sodium chloride. Pediatrics: 1.5 mg/kg diluted in 25 mL 0.9% sodium chloride and administered by intravenous infusion	Total cumulative dose: 1,000 mg Hemodialysis: 100 mg for 10 doses at consecutive dialysis session, as slow IV injection or as an infusion diluted in a 100mL of 0.9% NaCl over at least 15 minutes Non-Dialysis Dependent-Chronic Kidney Disease: 200 mg for 5 doses within the 14 day period as slow IV injection. Limited	Total cumulative dose: 1020 mg 510 mg intravenous injection followed by a second 510 mg intravenous injection 3 to 8 days later. Administer Feraheme as an undiluted intravenous injection delivered at a rate of up to 1 mL/sec (30 mg/sec).

	33 lbs): Total amount (mL) = 0.0442 (Desired Hb-Observed Hb) × W (kg) + (0.26 ×W) Each mL contains 50 mg of elemental iron. A test dose (0.5 mL) is required before the dosing.	over 1 hour per dialysis session. The maximum dosage should not exceed 125 mg per dose	experience with 500 mg for 2 doses on day 1 and day 14, diluted in a maximum of 250 mL of 0.9% NaCl, over a period of 3.5 to 4 hours. Peritoneal Dialysis: 300 mg for 2 doses 14 days apart, as infusion diluted in a maximum of 250mL of 0.9% NaCl. over 1.5 hours, followed by 400 mg infusion over 2.5 hours 14 days later.	

Reviewer's table

2.3 Availability of Proposed Active Ingredient in the United States

This drug has not been approved in the U.S. There are five intravenous iron products available in the U.S. as mentioned above.

2.4 Important Safety Issues with Consideration to Related Drugs

Intravenous iron products have been associated with anaphylactic-type reactions. Iron dextran products (INFeD and Dexferrum) have a boxed warning for anaphylactic-type reactions. Ferrlecit, Venofer and Feraheme have bolded warnings for hypersensitivity reactions.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Injectafer was initially submitted under NDA 22-054 on June 15, 2006 and the proposed indication was the treatment of iron deficiency anemia in patients with heavy uterine bleeding, post-partum anemia, inflammatory bowel disease and hemodialysis. The proposed dose regimen of Injectafer was 1000 mg as maximum single dose injection with a maximum total dose of 2500 mg. On July 9, 2007, a Not Approvable Letter was issued and stated that the supplied clinical data indicated that the proposed Ferinject dose regimen was accompanied with an unacceptable risk for death, serious adverse reactions and clinically important hypophosphatemia. The sponsor submitted a Complete Response on September 12, 2007 including additional clinical data from patients with chronic kidney disease. On November 14, 2007, the sponsor revised the proposed indication to the treatment of iron deficiency anemia in women with heavy uterine bleeding or post-partum patients with iron deficiency anemia. An Advisory Committee Meeting was held on February 1, 2008. The committee agreed that the available clinical data indicated Injectafer® was associated with a mortality disadvantage compared to oral iron and recommended an

unfavorable benefit-risk assessment for the proposed indication. The committee did consider the data as providing a favorable benefit-risk assessment for Injectafer in the treatment of iron deficiency anemia in post-partum women or women with heavy uterine bleeding who have had an unsatisfactory response to oral iron or were intolerant of oral iron.

The Agency issued a Not Approvable action on March 11, 2008. The letter indicated that the risk for mortality must be more thoroughly assessed and additional safety data should be obtained from clinical studies of Injectafer use among the applicable patient population of women who are intolerant to oral iron or who had an unsatisfactory response to oral iron. The Agency recommended that these studies use appropriate control groups in order to meaningfully interpret the data. The Agency stated that the proposed dosage regimen may deliver an excessive iron dose during a single administration and recommended that the sponsor consider the development of an alternate dosage regimen that delivers a lower (single dose) amount of iron.
A meeting was held on May 18, 2009 under IND 63,243 between the Agency and the sponsor to discuss the proposed further clinical studies (1VIT09031 and 1VIT09030) to evaluate the efficacy and safety of a low dose of Injectafer (maximum single dose of 750 mg with maximum total dose of 1500 mg) in patients who are intolerant to oral iron or who had an unsatisfactory response to oral iron with a oral iron run-in period and also in patients with chronic renal disease (CKD). The Agency agreed on the proposed studies and the proposed cardiovascular composite safety endpoint to be evaluated in these studies. In the proposed studies, other intravenous iron were selected as control in patients with CKD and in patients who are intolerant to oral iron. The Agency emphasized the double-blind design to assess the safety endpoint.

2.6 Other Relevant Background Information

FCM has been authorized for use and marketed in other countries by Vifor Pharma or a subsidiary company since 2007. It is currently registered under 3 different trade names: Ferinject®, Injectafer®, and Iroprem®, varying by country. As of 17 June 2011, the product is approved for use and marketed in 20 European countries. It has been approved but it has not yet been marketed in 15 other countries. The Summary of Product Characteristics in U.K. lists that Ferinject is indicated for treatment of iron deficiency when oral iron preparations are ineffective or cannot be used.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The NDA submission is an electronic submission in eCTD format. Four study sites with most patients enrolled in two pivotal clinical trials (two sites each in 1VIT09030 and 1VIT09031) were requested for inspection by the Office of Scientific Investigations. The results are pending.

3.2 Compliance with Good Clinical Practices

Informed consent was required from patients in all clinical trials. Independent ethics committees/institutional review boards at all participating centers were required to give permission for these studies.

3.3 Financial Disclosures

The sponsor certified that there was no financial arrangement with clinical investigators, who conducted the clinical studies 1VIT09030 and 1VIT09031 (Form FDA 3454). In several supportive studies conducted by Vifor, two principal investigators and one steering committee member received consulting fees from Vifor. Dr. (b) (6) received 27,500 (b) (6) (currency in Switzerland, equivalent to ~ $27,500)/year as consultant to Vifor and he enrolled (b) (6) patients in Study (b) (6) and (b) (6) patients in Study (b) (6). Dr. (b) (6) received 30,000 (b) (6) (equivalent to ~ $30,000)/year as consultant to Vifor and enrolled (b) (6) patients in Study (b) (6) and also served as steering committee member in Study (b) (6). Dr. (b) (6) received 30,000 (b) (6) (equivalent to ~ $30,000)/year as consultant to Vifor and served as steering committee members for Studies (b) (6).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

CMC review is pending.

4.2 Clinical Microbiology

Injectafer will be (b) (4) perating mechanism. No deficiencies were identified by FDA Clinical Microbiology reviewer (Stephen E. Langille, Ph.D., dated 5/8/2012).

4.3 Preclinical Pharmacology/Toxicology

The pharmacology and toxicology information was referenced the previous submission under NDA 22-054. No deficiencies were identified and the following are summaries from FDA Pharmacology/Toxicology reviewer (Yash M. Chopra, Ph.D., dated 6/5/2007) for NDA 22-054.

FCM, an intravenous hematinic preparation liberates utilizable iron in the body for intermittent use in iron deficient anemia. The released iron binds with iron binding proteins and accumulates mainly in animal's blood cells with about 76% in red cells, 11% in liver and 2% in spleen and 1% in kidney. Single intravenous doses of 1 g/kg and 0.24 g/kg in rats and dogs, respectively were not lethal but 2 g dose in mice was lethal. The repeat dose 13-week intravenous infusion toxicity study in rats and dogs showed iron deposition

in multiple organs including liver, spleen, lymph nodes and kidneys. The dose of 9 mg/kg/week was tolerated well in these species. Similar tissue deposition was also seen in a chronic continuous intravenous infusion 26-week study in dogs, 9 mg/kg/week was identified as a well tolerated dose. FCM was not genotoxic in a battery of tests including, *in vitro* microbial mutagenesis assay, *in vitro* chromosome aberration test in human lymphocytes, *in vitro* mammalian cell mutation assay in mouse lymphoma L5178Y/TK+/- cells, *in vivo* mouse micronucleus test. FCM exerted no adverse effect on the fertility and general reproductive performance in rats. It did not produce a teratogenic defect in pregnant rats but at a maternal toxic dose in rabbits, it caused fetal malformations (domed cranium with hydrocephaly). It did not produce perinatal and postnatal developmental defects in rat pups.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Injectafer contains iron in a stable ferric state as a complex with a carbohydrate polymer designed to release utilizable iron to the iron transport and storage proteins in the body (ferritin and transferrin).

4.4.2 Pharmacodynamics

The pharmacodynamic (PD) variables evaluated included total serum iron concentration, ferritin and transferrin concentrations, transferrin receptor concentrations, reticulocyte count and hemoglobin concentrations. No single PD variable was established as the primary PD factor. The percent increase in transferrin saturation for 500, 800, 1000 mg was 76, 63, 71%, respectively, at 24-36 hours post-dose. Iron binding capacity was fully utilized (as shown by 90% transferrin saturation) after doses of 500, 800 and 1000 mg.

The sponsor has not conducted thorough relevant QT or QTc interval prolongation studies.

4.4.3 Pharmacokinetics

An imaging study (VIT-IV-CL-001) used Fe-52 with positron imaging tomography (PET) and Fe-59 was conducted to assess the pharmacokinetics of FCM. Six patients with iron-deficiency anemia were enrolled. Subjects received a test dose of FCM 25 mg at least 1 week prior to the study and a 100 mg dose as ^{52}Fe and ^{59}Fe-labeled FCM, delivered over 10 minutes using a constant infusion pump in the study. The study showed that from 0 to 8 hours post-injection most of the FCM is found in the liver, spleen, and a much higher amount in bone marrow. Incorporation of radio iron in RBC increased rapidly during the first 6-9 days. The data for FCM in heart tissue was not available.

No distribution study was performed [redacted] (b) (4)

A dose escalation PK Study (VIT-IV-CL-02) in patients with mild iron deficiency anemia was performed to study safety and tolerability of the drug. The study included single IV doses of 100, 500, 800, and 1000 mg via a bolus IV injection or IV infusion. The geometric mean Cmax for total serum iron concentration did not increase linearly with dose (particularly in the 800 mg dose group). The average terminal half-life ($t_{1/2}$) of FCM (injected or infused) ranged from 10.3 h to 17.7 hours.

There were no PK studies conducted evaluating the effect of age, gender, race, or weight on FCM pharmacokinetics or studies in special population (renal or hepatic impaired).

No drug-drug interaction studies were conducted.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The following table lists the new studies completed after previous NDA (22-054) submission.

Table 2. New Studies Completed After Previous NDA Submissions

Studies Study Population	Study Design	Number of Subjects	Injectafer Dose
Primary Maximum 750 mg FCM Infusion Studies			
1VIT09031 IDA-broad population	Multicenter, randomized, open-label, controlled study	Total: 997 Cohort 1: FCM: 246; Oral iron: 253 Cohort 2: FCM: 253; IV Standard Care: 245	Maximum 750mg/dose Maximum total dose 1500 mg
1VIT09030 NDD-CKD	Multicenter, randomized, open-label, controlled study	Total: 2561 FCM: 1276 Venofer: 1285	
Other Maximum 750 mg FCM Infusion(s) Studies			
1VIT08021 IDA Non-dialysis dependent	Multicenter, randomized, open-label, controlled study	Total: 738 FCM: 370 Standard Medical Care: 368	750mg Single dose
1VIT08020 IDA	Multicenter, randomized, open-label, controlled study	Total: 161 FCM: 82 Iron Dextran: 79	Maximum 750mg/dose Maximum total dose 2250 mg
1VIT08019 IDA	Multicenter, randomized, open-label, controlled study	Total: 708 FCM: 348 Standard Medical Care: 360	
Other Short-Term Active-Controlled IDA Studies with Maximum FCM Doses Other than 750 mg			
1VIT07018 CKD	Multicenter, randomized, open-label, controlled study	Total 513 FCM: 254 Standard Medical Care: 259	Maximum 1000 mg/dose

1VIT07017 Postpartum or HUB	Multicenter, randomized, open-label, controlled study	Total: 2018 FCM: 996 Standard Medical Care: 1022	Maximum 1000 mg/dose
FER-IBD-COR IBD	Multicenter, randomized, open-label, controlled study	Total: 483 FCM: 244 Venofer: 239	Maximum 1000 mg/dose Maximum total: 2000 mg
Chronic Heart Failure Studies			
FER-CARS-02 CHF	Multicenter, randomized, blinded, controlled study	Total: 459 FCM: 304 Placebo: 155	200 mg
FER-CARS-03 CHF	Multicenter, randomized, observer-blinded, controlled study	Total: 34 FCM: 20 Placebo: 14	200mg

Reviewer's table

The following table lists the completed clinical studies submitted in previous NDA 22-054 that were included in the integrated mortality analysis.

Table 3. Completed Studies Submitted in Previous NDA

Studies Study population	Type of study	Number of Subjects	Maximum Single FCM Dose
1VIT03001 Postpartum women	Multicenter, randomized, open-label, controlled study	Total: 352 FCM: 174 Oral iron: 178	1000 mg Maximum total: 2500 mg
1VIT06011 Postpartum women	Multicenter, randomized, open-label, controlled study	Total: 289 FCM: 142 Oral Iron: 147	1000 mg Maximum total: 2500 mg
VIT-IV-CL-009 Postpartum women	Multicenter, randomized, open-label, controlled study	Total: 344 FCM: 227 Oral iron: 117	1000 mg Maximum total: 3000mg
1VIT04002/ 1VIT04003 HUB	Multicenter, randomized, open-label, controlled study	Total: 456 FCM: 230 Oral iron: 226	1000 mg Maximum total: 2500 mg
1VIT04004 NDD-CKD	Multicenter, randomized, open-label, controlled study	Total: 250 FCM: 147 Oral Iron: 103	1000 mg Maximum total: 2000 mg
VIT-IV-CL-015 HDD-CKD	Multicenter, randomized, open-label, controlled study	Total: 237 FCM: 119 Venofer®: 118	200mg
VIT-53214 HDD-CKD	Non-controlled study	Total: 162 FCM: 162	200mg
VII-IV-CL-008 IBD	Multicenter, randomized, open-label, controlled study	Total: 200 FCM: 137 Oral iron: 63	1000 mg Maximum total: 3000 mg
FER-CARS-01 CHF	Multicenter, randomized, blinded, controlled study	Total: 72 FCM: 30 Venofer: 27	200mg

VIT-IV-CL-003 IDA	Dose-finding, non-controlled study	Total: 46 FCM: 46	1000 mg

Reviewer's table

5.2 Review Strategy

Two randomized controlled trials (1VIT 09031 and 1VIT09030) were reviewed for efficacy for the proposed indications. All clinical data were reviewed for the safety.

5.3 Discussion of Individual Studies/Clinical Trials

Two pivotal studies (1VIT09031 and 1VIT09030) were submitted to support the efficacy and safety of Injectafer for the proposed indication and the proposed dose regimen of 15 mg/kg with the maximum individual dose of 750 mg and a total maximum cumulative dose of 1,500 mg over 2 infusions.

Study 1VIT09031 was a multicenter randomized, open-label, active-controlled study in patients with iron deficiency anemia (IDA). The study required a 14-day run-in period of oral iron treatment and included two cohorts of subjects. The Cohort 1 included subjects who had an inadequate response to oral iron treatment during the 14-day run-in period. The Cohort 2 included subjects who were intolerant to oral iron during the 14-day run-in period or who were deemed unsuitable by the Investigator for the oral iron. Subjects in Cohort 1 were randomized in a 1:1 ratio to receive either Injectafer (FCM) or continuation of oral iron for another 14 days. Subjects in Cohort 2 were randomized in a 1:1 ratio to receive either IV FCM or IV standard of care (other IV iron). The pre-specified primary efficacy endpoint was the mean change from baseline to the highest hemoglobin observed any time between baseline and Day 35 or time of intervention in Cohort 1.

Study 1VIT09030 was a multicenter, randomized, open-label, active controlled study that compared the safety and efficacy of FCM with Venofer in subjects with IDA and non-dialysis dependent chronic kidney disease. The primary efficacy endpoint was the mean change from baseline to the highest observed hemoglobin any time between baseline and end of treatment period (Day 56) or time of intervention.

Both Studies 1VIT 09031 and 1VIT09030 included pre-specified cardiovascular composite safety endpoints for safety evaluation for the proposed dosing regimen.

6 Review of Efficacy

Efficacy Summary

Two randomized controlled pivotal trials (1VIT09031 and 1VIT09030) were conducted to support the efficacy of Injectafer with the proposed dose regimen of 15 mg/kg with the maximum individual dose of 750 mg and a total dose of 1,500 mg. Study 1VIT09031 was

conducted in patients with iron deficiency anemia who had an inadequate response to oral iron treatment, who were intolerant to oral iron during the 14-day run-in period, or who were deemed unsuitable by the Investigator for the oral iron, mainly due to low hemoglobin level with or without co-morbidities. Study 1VIT09030 was conducted in patients with non-dialysis dependent chronic kidney disease (NDD-CKD). Both clinical studies were randomized, open-label, controlled studies. In Study 1VIT09031, oral iron was used as control in patients who had an inadequate response to oral iron treatment in Cohort 1 and other IV iron products (mostly Venofer) were used as control in patients who were intolerant to oral iron in Cohort 2. In Study 1VIT09030, Venofer was used as control in patients with CKD. The primary efficacy endpoint was the mean change from baseline to the highest hemoglobin observed anytime between baseline and Day 35 or time of intervention in Study 1VIT09031 and between baseline and Day 56 or time of intervention in Study 1VIT09030.

In Study 1VIT09031, the results show that the mean increase in hemoglobin from baseline to the highest value between baseline and Day 35 or time of intervention in the Injectafer group was statistically significantly greater than that in the oral iron group in Cohort 1 (1.57 g/dL vs. 0.80 g/dL, $p<0.01$) and also higher than that in the IV standard care group (2.90 g/dL vs. 2.16 g/dL, $p<0.01$) in Cohort 2. This study demonstrated that Injectafer increased hemoglobin level in patients with iron deficiency anemia who had an inadequate response to oral iron treatment or who were intolerant to oral iron.

In Study 1VIT09031, the mean increase in hemoglobin from baseline to the highest value between baseline and Day 56 or time of intervention in the Injectafer group was non-inferior to Venofer (1.13 g/dL vs. 0.92 g/dL, treatment difference 0.21 g/dL [95% CI 0.13-0.28 g/dL]). The results from the secondary efficacy endpoints analyses including hemoglobin response and iron indices were consistent with the primary efficacy analysis results in both studies. The results from subgroup analyses including baseline hemoglobin level and etiology of iron deficiency anemia in Study 1VIT09031 and baseline hemoglobin, EPO use and CKD stage in Study 1VIT09030 were all consistent with the results from the primary efficacy endpoint analyses. This study demonstrated that Injectafer increased hemoglobin level in patients with iron deficiency anemia in NDD-CKD population.

Efficacy results and analyses are presented in detail below.

6.1 Indication

The proposed indication is a broad indication for the treatment of iron deficiency anemia.

6.1.1 Method

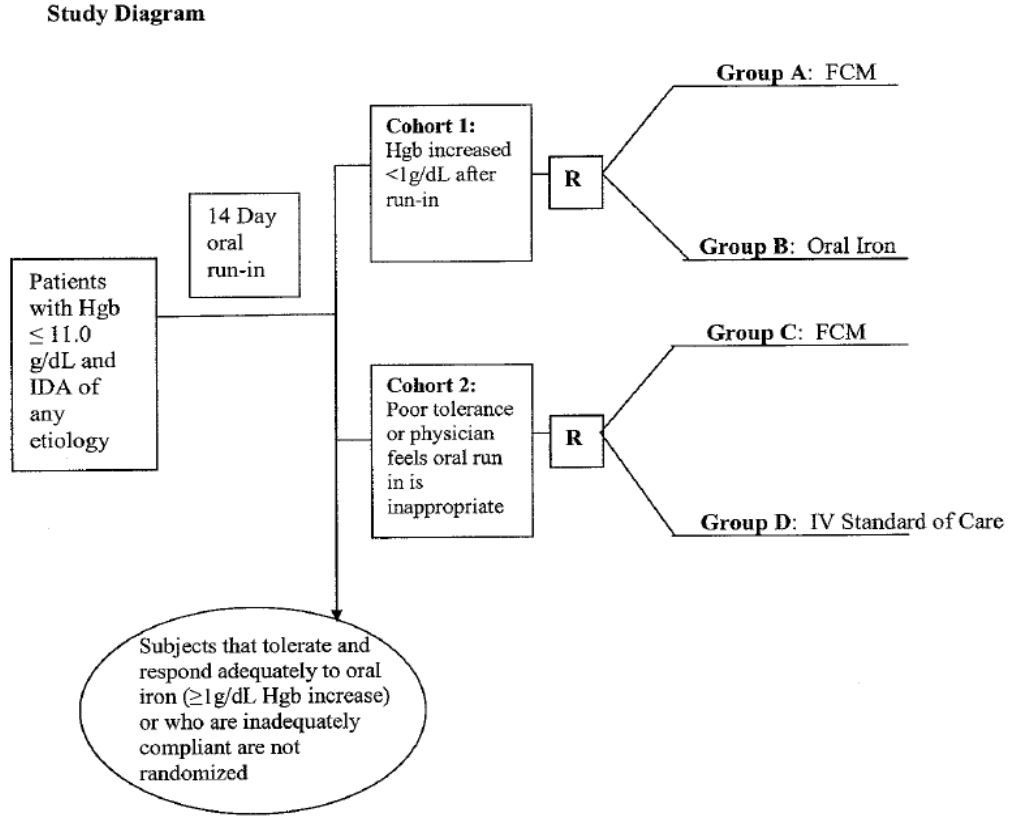
The sponsor conducted two randomized controlled studies (1VIT09031 and 1VIT09030) to evaluate the efficacy of Injectafer (FCM) for the proposed indication and the proposed dose

regimen of 15 mg/kg with the maximum individual dose of 750 mg and a total maximum cumulative dose of 1,500 mg over 2 infusions.

Study 1VIT09031

Study 1VIT09031 was a multicenter randomized, open-label, active-controlled study in patients with iron deficiency anemia (IDA). The study required a 14-day run-in period of oral iron treatment (Ferrous Sulfate 325 mg tablets [65 mg elemental iron], three times a day). The study included two cohorts of subjects. The Cohort 1 included subjects who had an inadequate response to oral iron treatment during the 14-day run-in period. The Cohort 2 included subjects who were intolerant to oral iron during the 14-day run-in period or who were deemed unsuitable by the Investigator for the oral iron. The study diagram is shown below.

Figure 1. Study Diagram of 1VIT09031



Sponsor's Figure

Cohort 1:

Cohort 1 included subjects who were found to have an unsatisfactory response to oral iron (defined as subjects whose Hgb values increases < 1 g/dL from baseline despite ≥ 67% compliance based on pill count), had transferrin saturation and ferritin values that continue

to meet the inclusion criteria (Hgb <12 g/dL, TSAT ≤ 30% and 100 ng/mL ≤ ferritin ≤ 300 ng/mL) and no exclusion criteria.

Subjects were stratified by etiology of their IDA (heavy uterine bleeding, gastrointestinal-disorders, and other), baseline Hgb level (≤ 9, 9.1-10.0, ≥ 10.1 g/dL), baseline cardiovascular risk (Category 0-1 vs. 2-3 as defined by the Framingham Model) at randomization.

Cardiac Risk Categories were based on the Framingham Heart Study Risk Model

0. No known risk factor
1. One of the following:
    - Age > 75 years
    - Current smoker
    - Hypertension or on a hypertension medication
    - Hyperlipidemia or use of a lipid lowering medicine
2. One of the following:
    - Diabetes
    - ≥2 of the risk factors used to define category 2
3. Prior history of cardiovascular disease

Subjects in Cohort 1 were randomized in a 1:1 ratio to receive either IV FCM or continuation of oral iron for another 14 days. Subjects who were less than 67% compliant were not randomized (unless the reduced compliance was due to poor tolerance, randomized in Cohort 2).

- Group A: FCM 15 mg/kg (postpartum subjects use pre-pregnancy weight) to a maximum of 750 mg per dose will be administered on Days 0 and 7 (for a total maximum cumulative dose of 1500 mg). It was administered as an undiluted IV push at 100 mg/minute.
- Group B: Ferrous Sulfate 325 mg p.o., three times a day for an additional 14 days.

Cohort 2:

Cohort 2 included subjects who were poorly tolerant or otherwise inappropriate for oral iron based on the following criteria:

- Subjects with documented adverse events of severe diarrhea, vomiting, constipation or abdominal pain due to the oral iron during the run in phase.
- Subjects who experienced other symptoms due to the oral iron during the run in phase had their dose of Ferrous Sulfate reduced to 325 mg p.o. once per day. Subjects who had hemoglobin increase < 1 g/dL on Day 14 (despite ≥ 67% compliance with the reduced dose schedule) or who continued to experience symptoms despite the reduced dose were included.
- Subjects whose physicians feel the subject is inappropriate for a 14 day course of oral iron (e.g., baseline Hgb is sufficiently low that the patient requires rapid repletion of iron

stores to minimize the risk of eventually needing a blood transfusion [e.g., Hgb < 8 g/dL unless there is evidence of cardiac or respiratory dysfunction in which case IV iron may be used without oral run-in if Hgb < 9 g/dL]) but who otherwise satisfy the entry criteria.

Subjects in Cohort 2 were randomized in a 1:1 ratio to receive either IV FCM or IV standard of care (other IV iron):

- Group C: FCM 15 mg/kg (postpartum subjects use pre-pregnancy weight) to a maximum of 750 mg per dose will be administered on Days 0 and 7 (for a total maximum cumulative dose of 1500 mg). It will be administered as an undiluted IV push at 100 mg/minute.

- Group D: IV standard of care (other IV iron) as determined by the study site physician.

The study objective of Cohort 1:

- To assess the mean increase from baseline to the highest observed hemoglobin value between baseline and Day 35 or time of intervention for patients taking FCM as compared to that for patients taking Ferrous sulfate for an additional 14 days

The study objective of Cohort 2:

- To assess the safety and tolerability of FCM as compared to IV standard of care after 120 days

The primary efficacy endpoint was the mean change from baseline to the highest observed hemoglobin observed any time between baseline and Day 35 or time of intervention in Cohort 1.

The secondary efficacy endpoints included:

In Cohort 2 only:

- Mean change from baseline to the highest observed hemoglobin observed any time between baseline and Day 35 or time of intervention

In Cohort 1 and 2:

- Proportion of subjects achieving a hemoglobin value >12 g/dL any time between baseline and Day 35 or time of intervention
- Mean change from baseline to the highest ferritin observed any time between baseline and Day 35 or time of intervention
- Proportion of subjects achieving a hemoglobin value >12 g/dL and an increase in ferritin ≥ 160 ng/mL any time between baseline and Day 35 or time of intervention. The two criteria do not need to be met on the same day.

- Proportion of subjects achieving an increase in hemoglobin value ≥ 2 g/dL any time between baseline and Day 35 or time of intervention.
- Mean change from baseline to each scheduled visit for hemoglobin, TSAT, and ferritin

Randomized subjects were to return for efficacy and safety evaluations on Days 7, 14 and 35. In addition, subjects were to be contacted by phone on day 90 and returned to the clinic on Day 120 to assess for adverse events.

Study 1VIT09030

Study 1VIT09030 was a multicenter, randomized, open-label, active controlled study that compared the safety and efficacy of FCM with Venofer in subjects with IDA and non-dialysis dependent chronic kidney disease. Patients must have a Hemoglobin ≤ 11.5 g/dL and chronically impaired renal function defined by either of the following criteria:

- GFR < 60 ml/min/1.73 m^2 on two measurements during the screening period (using the DRD calculation), or
- GFR < 90 ml/min/1.73 m^2 on two measurements during the screening period and either:
  - Kidney damage as indicated by abnormalities in composition of urine, or
  - Elevated risk of cardiovascular disease (Category 2 or 3) as defined by the Framingham Mode.

Other inclusion criteria included TSAT ≤ 30%, 100 ng/mL ≤ ferritin ≤ 300 ng/mL, a stable ESA dose (±20%) for 4 week prior to randomization if subject was on an ESA.

Study patients were stratified by baseline Hgb level (≤ 9, 9.1-10.0, ≥ 10.1 g/dL), baseline cardiovascular risk (have a history of MI, stroke, or CHF yes or no), country/region, erythropoietin use (yes/no), and CKD stage as per National Kidney Foundation Outcome Quality Initiative (K/DOQI) stage of chronic kidney disease (1-2, 3-4, or 5).

Study patients were randomized in a 1:1 ratio to receive either IV FCM or IV Venofer.

- FCM Group: FCM 15 mg/kg to a maximum of 750 mg per dose for a maximum total dose of 1500 mg.
- Venofer Group: Venofer 200 mg for 5 doses with a total dose of 1000 mg.

The primary efficacy endpoint was the mean change from baseline to the highest observed hemoglobin any time between baseline and end of treatment period (Day 56) or time of intervention.

Randomized subjects returned for efficacy and safety evaluations on Days 3, 7, 11, 14, 28, and 56.

6.1.2 Demographics

Study 1VIT09031

The mean age of study subjects was 43 years. More than 94% of study subjects were females. More African American (39%) were included in Cohort 1 and more Caucasians (>50%) were included in Cohort 2. There were no clinically significant differences in demographic characteristics between two treatments in both cohorts (see Table below).

Table 4. Demographic Characteristics in Study 1VIT09031

Demographic Characteristics	Cohort 1		Cohort 2	
	FCM (N=246)	Oral Iron (N=253)	FCM (N=253)	IV SC (N=245)
Age (years)				
Mean (SD)	43.1 (17.2)	43.5 (17.7)	43.6 (16.9)	42.6 (15.5)
Median	41	41	41	42
Minimum, Maximum	18,94	18,92	18,90	18,85
≤ 65	214 (87.0%)	218 (86.2%)	220 (87.0%)	222 (90.6%)
66-75	16 (6.5%)	17(6.7%)	19 (7.5%)	12 (4.9%)
>76	16 (6.5%)	18 (7.1%)	14 (5.5%)	11 (4.5%)
Gender				
Female	233 (94.7%)	238 (94.1%)	239 (94.5%)	231 (94.3%)
Male	13 (5.3%)	15 (5.9%)	14 (5.5%)	14(5.7%)
Race				
African American	95 (38.6%)	98 (38.7%)	63 (24.9%)	62 (25.3%)
Asian	2 (0.8%)	1 (0.4%)	0	3 (1.2%)
Caucasian	67 (27.2%)	79 (31.2%)	135 (53.4%)	136 (55.5%)
Hispanic	79 (32.1%)	69 (27.3%)	51 (20.2%)	41 (16.7%)
Other	3 (1.2%)	6 (2.4%)	4 (1.6%)	3 (1.2%)

SD=standard deviation
Reviewer's table

In study patients, the primary etiology of IDA was heavy uterine bleeding (HUB), followed by gastrointestinal (GI) disorders. The mean hemoglobin (Hgb) at baseline was around 9-10 g/dL with the mean TSAT about 10-20% and the mean ferritin of 30 ng/ml or less. More than 50% of study patients had TSAT <20% and over 90% of patients had ferritin <100 ng/mL. Patients in Cohort 2 had more severe IDA as compared to those in Cohort 2 based on Hgb, TSAT and ferritin levels. No patients in Cohort 1 and few patients in Cohort 2 were EPO users. About one half of patients in Cohort 1 and over 70% of patients in Cohort 2 had received previous iron therapy and the majority of patients had no history of iron intolerance or drug allergy in both cohorts. The majority of subjects in each group had a cardiovascular risk category of 0-1with the most common cardiac risk factor of hypertension or on hypertension medication. There were no significant differences in baseline characteristics between the two treatment groups in both cohorts (see Table below).

Table 5. Baseline Characteristics in Study 1VIT09031

Baseline Characteristics	Cohort 1		Cohort 2	
	FCM (N=246)	Oral Iron (N=253)	FCM (N=253)	IV SC (N=245)
Etiology of IDA				
HUB	126 (51.2%)	124 (49.0%)	111 (43.9%)	109 (44.5%)
GI disorders	26 (10.6%)	27 (10.7%)	59 (23.3%)	56 (22.9%)
Other	94 (38.2%)	102 (40.3%)	83 (32.8%)	80 (32.7%)
Baseline Hemoglobin (g/dL)				
Mean (SD)	10.6 (1.0)	10. 6 (1.1)	9.1 (1.6)	9.0 (1.5)
Hemoglobin Category				
≤ 9 .0 g/d	23 (9.3%)	24 (9.5%)	122 (48.2%)	120 (49.0%)
9.1-10.0 g/dL	48 (19.5%)	48 (19.0%)	60 (23.7%)	60 (24.5%)
≥10.1 g/dL	175 (71.1%)	181 (71.5%)	71 (28.1%)	65 (26.5%)
Baseline TSAT (%)				
Mean (SD)	22.1 (14.8)	22.4 (15.1)	11.5 (12.2)	10.3 (9.7)
<20%	129 (52.4%)	129 (51.0%)	208 (82.2%)	213 (86.9%)
Baseline Ferritin (ng/mL)				
Mean (SD)	31.3 (67.7)	28.2 (39.2)	25.9 (63.8)	14.9 (29.3)
<100 ng/mL	233 (94. 7%)	240 (94.9%)	238 (94.1%)	241 (98.4%)
EPO Use				
No	246 (100.0%)	253 (100.0%)	248 (98.0%)	240 (98.0%)
Yes	0	0	5 (2.0%)	5 (2.0%)
Previous Iron Therapy				
No	117(47.6%)	113 (44.7%)	67 (26.5%)	62 (25.3%)
Yes	129 (52.4%)	140 (55.3%)	186 (73.5%)	183 (74.7%)
History of Iron Intolerance				
No	241 (98.0%)	248 (98.0%)	183 (72.3%)	175 (71.4%)
Yes	5 (2.0%)	5 (2.0%)	70 (27.7%)	70 (28.6%)
History of Drug Allergy				
No	187 (76.0%)	191 (75.5%)	174 (68.8%)	161 (65.7%)
Yes	59 (24.0%)	62 (24.5%)	79 (31.2%)	84 (34.3%)
Cardiovascular Risk Category				
0-1	191 (77.6%)	185 (73.1%)	200 (79.1%)	188 (76.7%)
2-3	55 (22.4%)	68 (26.9%)	53 (20.9%)	57 (23.3%)
Presence of Cardiac Risk Factors				
Any cardiac risk factor	100 (40. 7%)	107 (42.3%)	103 (40 .7%)	104 (42.4%)
Age >75 years	16 (6.5%)	19 (7.5%)	14 (5.5%)	12 (4.9%)
Prior history of cardiovascular disease	13 (5.3%)	17(6.7%)	24 (9.5%)	18 (7.3%)
Current smoker	14 (5.7%)	17 (6.7%)	25 (9.9%)	21 (8.6%)
Hypertension/on hypertension meds	72 (29.3%)	77 (30.4%)	65 (25.7%)	70 (28.6%)
Hyperlipidemia/on lipid-lowering agent	35 (14.2%)	43 (17.0%)	36 (14.2%)	38 (15.5%)
Diabetes	34 (13.8%)	48 (19.0%)	25 (9.9%)	28 (11.4%)

SD=standard deviation
Reviewer's table

Over 65% of subjects assigned to Cohort 2 were due to being inappropriate for oral iron treatment as deemed by physician (e.g., low hemoglobin requiring rapid correction [defined as <8 g/dL or <9 g/dL, with evidence of cardiovascular or pulmonary dysfunction]) for both Group C (FCM) and Group D (IV SC) (see Table below).

Table 6. Reasons for Subjects Assigned to Cohort 2 in Study 1VIT09031

Reason Assigned (Cohort 2)	Cohort 2	
	Group C FCM (N=253)	Group D IVSC (N=245)
Inappropriate for oral iron (e.g., low hemoglobin)	169 (66.8%)	168 (68. 6%)
Severe intolerance to oral iron during the run-in phase	62 (24.5%)	60 (24.5%)
Inadequate response to oral iron after dose reduction	20 (7.9%)	16 (6.5%)
Missing	2 (0.8%)	1 (0.4%)

Reviewer's table

For subjects randomized to Group D (IV SC), the majority (89.8%) of patients received Venofer as intravenous iron product.

Table 7. Intravenous Iron Products Received in the Control Group in Cohort 2 in Study 1VIT09031

Type of Iron	Group D IVSC (N=245) n(%)
Venofer	220 (89.8%)
Iron Dextran	20 (8.2%)
Ferrlecit	3 (1.2%)
Dexferrum	2 (0.8%)
Feraheme	1 (0.4%)
INFed	1 (0.4%)

Reviewer's table

Study 1VIT09030

The mean age of study patients was 67 years in both treatment groups and the majority of patients were >65 years of age. There were more females (64%) than males. Over a half of patients were Caucasian (54%). No clinically significant differences in the demographic characteristics were observed between the FCM and Venofer groups (see Table below)

Table 8. Demographic Characteristics in Study 1VIT09030

Demographic Characteristic	FCM (N=1276)	Venofer (N=1285)	Total (N=2561)
Age (years)			
Mean (SD)	67.5 (13.0)	67.2 (13.0)	67.3 (13.0)
Median	69	69	69
Minimum, Maximum	19, 96	24, 101	19, 101
≤ 65	500 (39.2%)	536 (41.7%)	1036 (40.5%)
66-75	395 (31.0%)	394 (30.7%)	789 (30.8%)
>76	381 (29.9%)	355 (27.6%)	736 (28.7%)
Gender			
Female	810 (63.5%)	818 (63.7%)	1628 (63.6%)
Male	466 (36.5%)	467 (36.3%)	933 (36.4%)
Race			
African American	334 (26.2%)	325 (25.3%)	659 (25.7%)
Asian	20 (1.6%)	21 (1.6%)	41 (1.6%)
Caucasian	676 (53.0%)	693 (53.9%)	1369 (53.5%)
Hispanic	234 (18.3%)	236 (18.4%)	470 (18.4%)
Other	12 (0.9%)	10 (0.8%)	22 (0.9%)

SD=standard deviation
Reviewer's table

The majority of patients were in CKD stage 3-4 (86%) and were not current EPO users (82.0%). The mean Hgb of patients was 10 g/dL with the mean TSAT of 20% and the mean ferritin of 74 ng/mL. About one half of patients had received previous iron therapy (54%) and the majority of them had no history of iron intolerance (95%) or drug allergy (55%). Among the patients who had history of iron intolerance, the most patients were intolerant to oral iron and only five were intolerant to specified IV iron products. The most common symptom associated with intolerance to iron products prior to study enrollment was constipation. The majority of subjects in both groups had no history of myocardial infarction, stroke, or congestive heart failure. The patients' baseline characteristics were similar between the two treatment groups (see Table below).

Table 9. Baseline Characteristics in Study 1VIT09030

Baseline Characteristics	FCM (N=1276)	Venofer (N=1285)	Total (N=2561)
CKD Stage			
2	68 (5.3%)	78(6.1%)	146 (5.7%)
3-4	1113 (87.2%)	1105 (86.0%)	2218 (86.6%)
5	95 (7.4%)	102 (7.9%)	197 (7.7%)
EPO Use			
No	1046 (82.0%)	1057 (82.3%)	2103 (82.1%)
Yes	230 (18.0%)	228 (17.7%)	458 (17.9%)
Baseline Hemoglobin (g/dL)			
Mean (SD)	10.3 (0.8)	10.3 (0.8)	10.3 (0.8)

Hemoglobin Category			
≤ 9 .0 g/d	103(8.1%)	102 (7.9%)	205 (8.0%)
9.1-10.0 g/dL	286 (22.4%)	292 (22.7%)	578 (22.6%)
≥10.1 g/dL	887 (69.5%)	891 (69.3%)	1778 (69.4%)
Baseline TSAT (%)			
Mean (SD)	19.8 (7.8)	19.6 (7.4)	19.7(7.6)
<20	660 (51.7%)	662 (51.5%)	1322 (51.6%)
Baseline Ferritin (ng/mL)			
Mean (SD)	73.0 (64.6)	75.15(64.1)	74.0 (64.4)
<100	955 (74.8%)	943 (73.4%)	1898 (74.1%)
Baseline GFR-MDRD			
Mean (SD)	32.5 (14.7)	32.27 (14. 9)	32.4 (14.8)
Previous Iron Therapy			
No	580 (45.5%)	592 (46.1%)	1172 (45.8%)
Yes	696 (54.5%)	693 (53.9%)	1389 (54.2%)
History of Iron Intolerance			
No	1209 (94.7%)	1222 (95.1%)	2431 (94.9%)
Yes	67 (5.3%)	63 (4.9%)	130(5.1%)
History of Drug Allergy			
No	705 (55.3%)	698 (54.3%)	1403 (54.8%)
Yes	571 (44.7%)	587 (45.7%)	1158 (45.2%)
History of Myocardial Infarction			
No	1079 (84.6%)	1101 (85.7%)	2180(85.1%)
Yes	197 (15.4%)	184 (14.3%)	381 (14.9%)
History of Stroke			
No	1111 (87.1%)	1128 (87.8%)	2239 (87.4%)
Yes	165 (12.9%)	157 (12.2%)	322 (12.6%)
History of Congestive Heart Failure			
No	961 (75.3%)	976 (76.0%)	1937 (75.6%)
Yes	315 (24.7%)	309 (24.0%)	624 (24.4%)

SD=standard deviation
Reviewer's table

6.1.3 Subject Disposition

Study 1VIT09031

During the oral iron run-in period, a total of 1497 subjects received oral iron and of them 699 patients were further enrolled in the study.

A total of 1011 subjects were randomized from 84 centers in the US. These included 699 subjects who had an oral iron run-in period and 312 subjects who didn't have a run-in period and enrolled to Cohort 2 directly. Of the randomized 1011 subjects, 507 subjects enrolled in Cohort 1 (FCM: 250 subjects, oral iron: 257 subjects) and 504 subjects enrolled in Cohort 2 (FCM: 253 subjects, IV Standard care: 251 subjects).

Of the randomized 1011 subjects, 14 subjects (1.3%) were discontinued from the study prior to dosing. These subjects did not take study drug due to lost to follow up or other reasons. These 14 subjects were excluded from both efficacy and safety analysis.

Among the remaining 997 subjects, 977 (98%) patients who had received at least one dose of treatment and had at least one post-baseline hemoglobin assessment were included in the efficacy analysis, as modified intention to treat (mITT) population.

In the study, 807 (81%) subjects completed treatment phase (to Day 35) and 783 (79%) completed the study as scheduled (to Day 120). The most common reasons for discontinuation from the treatment phase were under selection criteria/compliance category (13%), due to violation of entry criteria or Day 35 Visit not within 5 days after Day 35, and lost to follow-up (3.6%).The detailed information on the study selection criteria/compliance was not captured in the case report form. Others were due to subject request (1.2%) and adverse events (1.1%). The most common reasons for discontinuation from the study as scheduled (Day 120) were due to study compliance (12%) and lost to follow-up (5.9%). The subject dispositions were similar between two treatments in both cohorts (see Table below).

Table 10. Subject Disposition in Study 1VIT09031

	Cohort 1		Cohort 2		Total
	FCM	Oral Iron	FCM	IV SC	
Subjects Randomized	250	257	253	251	1011
Subjects Treated (Safety Population)	246	253	253	245	997
mITT Population	244 (99.2%)	251 (99.2%)	245 (96.8%)	237 (96.7%)	977 (98.0%)
Subjects Completed Treatment Phase (Screening -Day 35)	196 (79.7%)	206 (81.4%)	210 (83.0%)	195 (79.6%)	807 (80.9%)
Subjects Did Not Complete Treatment Phase	50 (20.3%)	47 (18.6%)	43 (17.0%)	50 (20.4%)	190 (19.1%)
Adverse event	4 (1.6%)	1 (0.4%)	2 (0.8%)	4(1.6%)	11 (1.1%)
Selection criteria/compliance	32 (13.0%)	33 (13.0%)	31 (12.3%)	33 (13.5%)	129 (12.9%)
Lost to follow-up	9 (3.7%)	10 (4.0%)	7 (2.8%)	10 (4.1%)	36 (3.6%)
Subject request	5 (2.0%)	3 (1.2%)	2 (0.8%)	2 (0.8%)	12 (1.2%)
Other	0	0	1 (0.4%)	1 (0.4%)	2 (0.2%)
Subjects with Interventions (Day 0- Day 35)	4 (1.6%)	9 (3.6%)	4 (1.6%)	4(1.6%)	21 (2.1%)
Blood transfusion	1 (0.4%)	4 (1.6%)	2 (0.8%)	2 (0.8%)	9 (0.9%)
IV iron outside of protocol	1 (0.4%)	2 (0.8%)	0	1 (0.4%)	4 (0.4%)
Oral iron outside of protocol	2 (0.8%)	3 (1.2%)	2 (0.8%)	1 (0.4%)	8 (0.8%)
Subjects Completed Study as Scheduled (Screening -Day 120)	200 (81.3%)	204 (80.6%)	192 (75.9%)	187 (76.3%)	783 (78.5%)

Subjects Did Not Complete Study as Scheduled (Screening -Day 120)	46 (18.7%)	49 (19.4%)	61 (24.1%)	58 (23 .7%)	214 (21.5%)
Adverse event	2 (0.8%)	3 (1.2%)	4 (1.6%)	4(1.6%)	13 (1.3%)
Study compliance	26 (10.6%)	24 (9.5%)	35 (13.8%)	35 (14.3%)	120 (12.0%)
Lost to follow-up	12 (4.9%)	18 (7.1%)	14 (5.5%)	15 (6.1%)	59 (5.9%)
Subject request	4 (1.6%)	4 (1.6%)	3 (1.2%)	1 (0.4%)	12 (1.2%)
Physician decision	1 (0.4%)	0	0	0	1 (0.1%)
Other	1 (0.4%)	0	5 (2.0%)	3 (1.2%)	9 (0.9%)

Note: Percentages are based on the Safety Population.
Reviewer's table

In the study, 21 subjects received a blood transfusion (9 subjects) or iron product outside of the protocol (4 received IV iron and 8 received oral iron).

Study 1VIT09030

A total of 2584 subjects from 187 centers in U.S. were randomized to receive FCM (1290 subjects) or Venofer (1294 subjects). Of these 2584 subjects, 14 in the FCM group and 9 in the Venofer group were discontinued from the study prior to dosing. The reasons for discontinuation were due to subject request or selection criteria/study compliance.

Among the remaining 2561 subjects, 2493 (97%) patients who had received at least one dose of treatment, had at least one post-baseline hemoglobin assessment and had stable (within 20%) EPO dosing for 4 weeks were included in the efficacy analysis, as modified intention to treat (mITT) population.

A total of 1048 (82.1%) of the 1276 subjects in the FCM group and 1042 (81.1%) of the 1285 subjects in the Venofer group completed the Treatment Phase as scheduled (Screening - Day 56). The most common reasons for discontinuation from the treatment phase were due to selection criteria/compliance (14%), followed by adverse events (1.65), and subject request (1%). There was no difference between the two treatment groups. The subjects in both groups who discontinued due to selection criteria/study compliance were found to have either violated entry criteria or completed their Day 56 Visit early or had their Day 56 Visit performed >5 days after the protocol scheduled Day 56 Visit was to occur.

A total of 1059 (83.0%) of the 1276 subjects in the FCM group and 1073 (83.5%) of the 1285 subjects in the Venofer group completed the study as scheduled (Screening -Day 120). The most common reasons for discontinuation from the study as scheduled were due to study compliance (10.5%), adverse events (2.5%) and lost to follow-up (1.8%).

Fewer subjects from each group completed the Treatment Phase as scheduled than completed the study as scheduled because the 2 completion categories had different criteria. In order to have been considered to have completed the Treatment Phase as scheduled, a subject had to have received a dose of FCM or Venofer and completed the Day 56 Visit. In order to have completed study as scheduled, the subject only needed to have at least 1 dose of FCM or Venofer and a safety follow-up on Days 120-125. If a subject chose to

withdraw from the trial, the study site personnel asked to contact the subject at Day 120 for safety and if the subject agreed, he/she was considered as having completed the study.

One hundred (7.8%) subjects in the FCM group and 96 (7.5%) subjects in the Venofer group received an intervention during the study and the most of them were due to EPO dose increase (5.6% and 4.7%, respectively).

Table 11. Subject Disposition in Study 1VIT09030

Subject Disposition	FCM	Venofer	Total
Subjects Randomized	1290	1294	2584
Subjects Treated (Safety Population)	1276	1285	2561
mITT Population[a]	1249 (97.9%)	1244 (96.8%)	2493 (97.3%)
Subjects Completed Treatment Phase as Scheduled (Screening -Day 56)	1048 (82.1%)	1042 (81.1%)	2090 (81.6%)
Subjects Did Not Complete Treatment Phase as Scheduled (Screening - Day 56)	228 (17.9%)	243 (18.9%)	471 (18.4%)
Adverse event	20 (1.6%)	22 (1.7%)	42 (1.6%)
Selection criteria/compliance	181 (14.2%)	188 (14.6%)	369 (14.4%)
Lost to follow-up	11 (0.9%)	10 (0.8%)	21 (0.8%)
Subject request	9 (0.7%)	17(1.3%)	26 (1.0%)
Physician decision	3 (0.2%)	2 (0.2%)	5 (0.2%)
Other	4 (0.3%)	4 (0.3%)	8 (0.3%)
Subject Had an Intervention[b]	100 (7.8%)	96 (7.5%)	196 (7.7%)
Increased dose of EPO (Day 0 - Day 56)	71 (5.6%)	60 (4.7%)	131(5.1%)
Blood transfusion	15 (1.2%)	22 (1.7%)	37(1.4%)
IV iron outside of protocol	4 (0.3%)	5 (0.4%)	9 (0.4%)
Oral iron outside of protocol	10 (0.8%)	17(1.3%)	27 (1.1%)
Start dialysis	15 (1.2%)	4 (0.3%)	19 (0.7%)
Subjects Completed Study as Scheduled (Screening- Day 120)	1059 (83.0%)	1073 (83.5%)	2132 (83.2%)
Subjects Did Not Complete Study as Scheduled (Screening- Day 120)	217 (17.0%)	212 (16.5%)	429 (16.8%)
Adverse event	35 (2.7%)	30 (2.3%)	65 (2.5%)
Study compliance	138 (10.8%)	131 (10.2%)	269 (10.5%)
Lost to follow-up	23 (1.8%)	23 (1.8%)	46 (1.8%)
Subject request	17(1.3%)	22 (1.7%)	39(1.5%)
Physician decision	2 (0.2%)	1 (0.1%)	3 (0.1%)
Other	2 (0.2%)	5 (0.4%)	7 (0.3%)

Note: Percentages are based on the Safety Population.
a All subjects in the Safety Population who had at least 1 post-baseline hemoglobin assessment and had stable (within 20%) EPO dosing for 4 weeks, which may have included a dose of 0, before randomization.
b Subjects could have had multiple interventions.
Reviewer's table

6.1.4 Analysis of Primary Endpoint(s)

Study 1VIT09031

The primary efficacy endpoint in Cohort 1 was the mean change from baseline to the highest hemoglobin observed anytime between baseline and Day 35 or time of intervention. The

mean increase in hemoglobin in the FCM group was statistically significantly greater than that in the oral iron group (1.57 g/dL vs. 0.80 g/dL, p<0.01).

The sponsor also performed a post hoc comparison of Group C (FCM) versus Group D (IV Standard Care, IVSC) in Cohort 2. It also showed a statistically significantly greater mean increase in hemoglobin from baseline to the highest value between baseline and Day 35 or time of intervention in the FCM group than that in the IV standard care group (2.90 g/dL vs. 2.16 g/dL, p<0.01). See Table below.

Table 12. The Results of the Primary Efficacy Endpoint in Study 1VIT09031

Hemoglobin [Mean(SD)]	Cohort 1		Cohort 2	
	FCM (N=244)	Oral Iron (N=251)	FCM (N=245)	IV SC• (N=237)
Baseline Highest Value Change to Highest Value (35 Days)	10.6 (1.01) 12.2 (1.11) 1.57 (1.19)	10.6 (1.03) 11.4(1.18) 0.80 (0.80)	9.1 (1.60) 12.0 (1.22) 2.90 (1.64)	9.0 (1.47) 11.2 (1.26) 2.16 (1.25)
p-value	<0.01		<0.01	

Reviewer's table

Study 1VIT09030

The primary efficacy endpoint was the mean change from baseline to the highest observed hemoglobin any time between baseline and end of treatment period (Day 56) or time of intervention.

The mean increase in hemoglobin from baseline to the highest value between baseline and Day 56 or time of intervention demonstrated the non-inferiority with pre-specified non-inferiority margin of -0.2 g/dL (i.e., lower limit of 2-sided 95% CI of treatment comparison was ≥ -0.2) of FCM to Venofer.

Table 13. The Results of the Primary Efficacy Endpoint in Study 1VIT09030

Hemoglobin (g/dL) Mean (SD)	FCM (N=1249)	Venofer (N=1244)
Baseline Highest Value Change to Highest Value (56 days)	10.3 (0.8) 11.4 (1.2) 1.13 (1.04)	10.3 (0.8) 11.3 (1.1) 0.92 (0.92)
Treatment Difference: 95% CI	0.21 (0.13, 0.28)	

SD=standard deviation; CI=confidence interval
Reviewer's table

6.1.5 Analysis of Secondary Endpoints(s)

Study 1VIT09031

Hemoglobin >12.0 g/dL
In both Cohorts, the proportion of subjects with a hemoglobin value >12.0 g/dL anytime between baseline and Day 35 or time of intervention was statistically significantly greater in the FCM groups (57% in Cohort 1 and 51% in Cohort 2) than that observed in the comparator groups (29% in oral iron and 25% in IV SC).

Clinically Meaningful Increase in Hemoglobin
In both Cohorts, the proportion of subjects with a clinically meaningful increase in hemoglobin (defined as ≥ 1 g/dL for CKD, ≥ 2 g/dL for HUB or GI disorders, ≥ 3 g/dL for postpartum, and ≥ 2 g/dL for others) anytime between baseline and Day 35 or time of intervention was greater in the FCM groups (33% in Cohort 1 and 67% in Cohort 2) than that observed in the comparator groups (9% in oral iron and 48% in IV SC).

Hemoglobin >12.0 g/dL and an Increase in Ferritin ≥ 160 ng/mL
In each Cohort, the proportion of subjects with a hemoglobin value >12.0 g/dL and an increase in ferritin ≥160 ng/mL anytime between baseline and Day 35 or time of intervention was greater in the FCM groups (55% in Cohort 1 and 48% in Cohort 2) than that observed in the comparator groups (0.4% in oral iron and 6% in IV SC).

The results of these secondary efficacy endpoints are shown in the table below.

Table 14. Results of Secondary Efficacy Endpoints in Study 1VIT09031

Secondary Efficacy Endpoints	Cohort 1		Cohort 2	
	FCM (N=244)	Oral Iron (N=251)	FCM (N=245)	IV SC (N=237)
Hemoglobin >12.0 g/dL	139/244 (57.0%)*	73/251 (29.1%)	124/245 (50.6%)*	58/237 (24.5%)
Clinically meaningful increase in hemoglobin	80/244 (32.8%)*	22/251 (8.8%)	164/245 (66.9%)*	113/237 (47.7%)
Hemoglobin >12 g/dL and an increase in ferritin ≥ 160 ng/mL	133/244 (54.5%)*	1/251 (0.4%)	118/245 (48.2%)*	14/237 (5.90%)

*P<0.05
Reviewer's table

Mean Change in Hemoglobin and Iron Indices
In both Cohorts, the mean increases in hemoglobin, ferritin and TSAT from baseline to Day 35 or time of intervention were greater in the FCM groups as compared to those in the comparator groups (oral iron and IV SC) (see Table below).

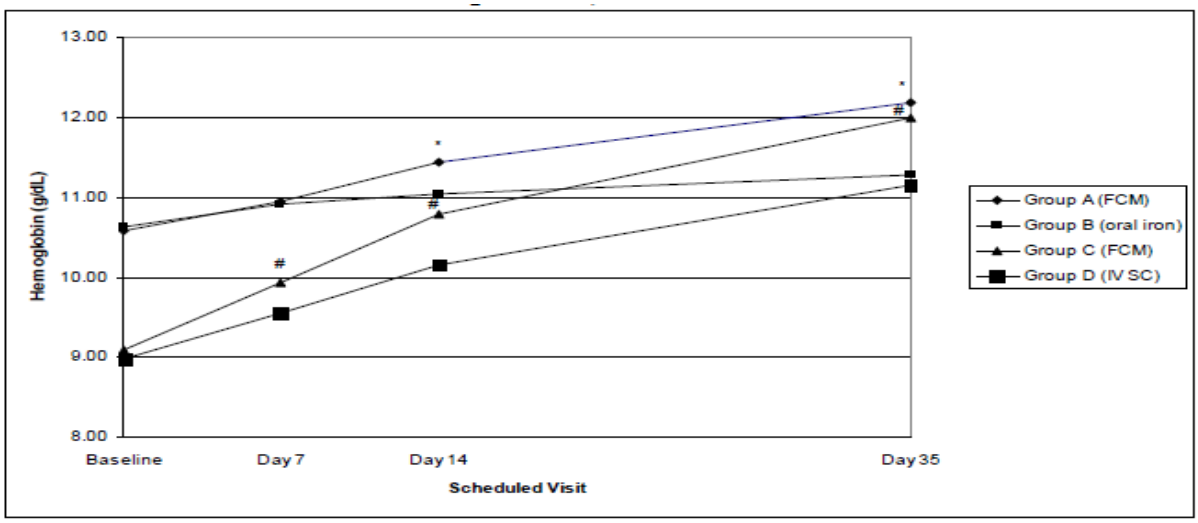
Table 15. Mean Changes in Hemoglobin and Iron Indices in Study 1VIT09031

Mean Changes	Cohort 1		Cohort 2	
	FCM	Oral Iron	FCM	IV SC
Mean change (SD) in Hgb (g/dL)	1.6 (1.2) (N=199)	0.6 (0.8) (N=204)	2.9 (1.7) (N=220)	2.1 (1.3) (N=202)
Mean change (SD) in Ferritin (ng/mL)	264.2 (224.2) (N=200)	-3.8 (26.7) (N=207)	218.2 (211.4) (N=223)	74.7 (115.7) (N=204)
Mean change (SD) in TSAT (%)	13.0 (16.3) (N=199)	-5.7 (15.9) (N=204)	20.18 (15.5) (N=221)	8.8 (12.7) (N=205)

Reviewer's table

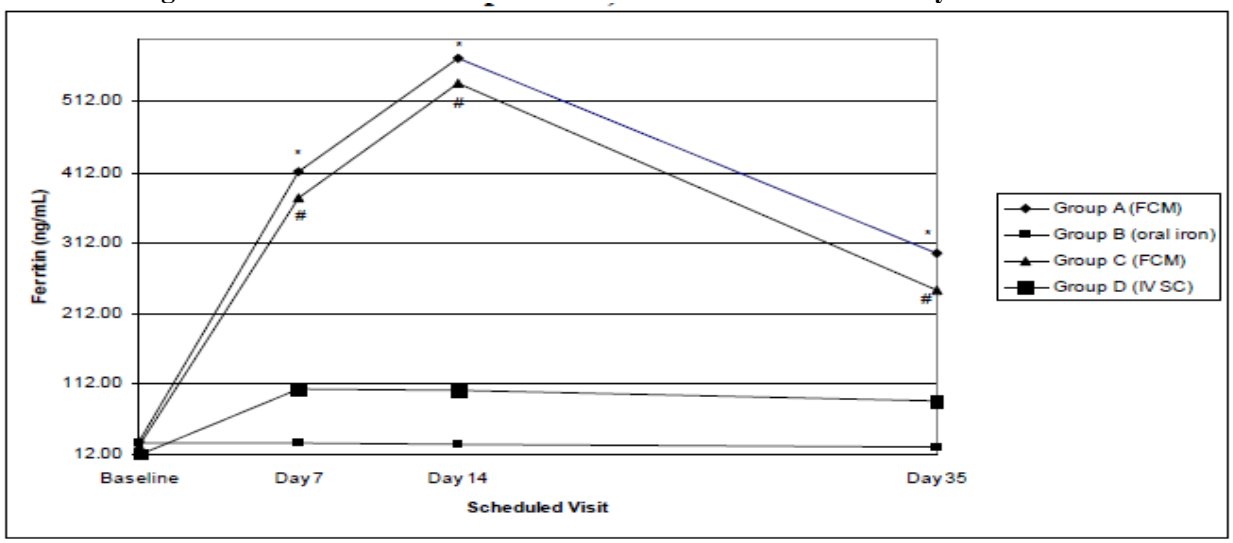
Mean changes in hemoglobin, ferritin and TSAT at each visit
Mean hemoglobin, ferritin, and TSAT values at each scheduled visit by treatment are presented in Figures below. Mean Ferritin and TSAT reached to the highest values at Day 14 and the mean hemoglobin level increased gradually over the time to the highest value at Day 35 for all treatment groups.

Figure 2. Mean Hemoglobin Values at Each Scheduled Visit in Study 1VIT09031



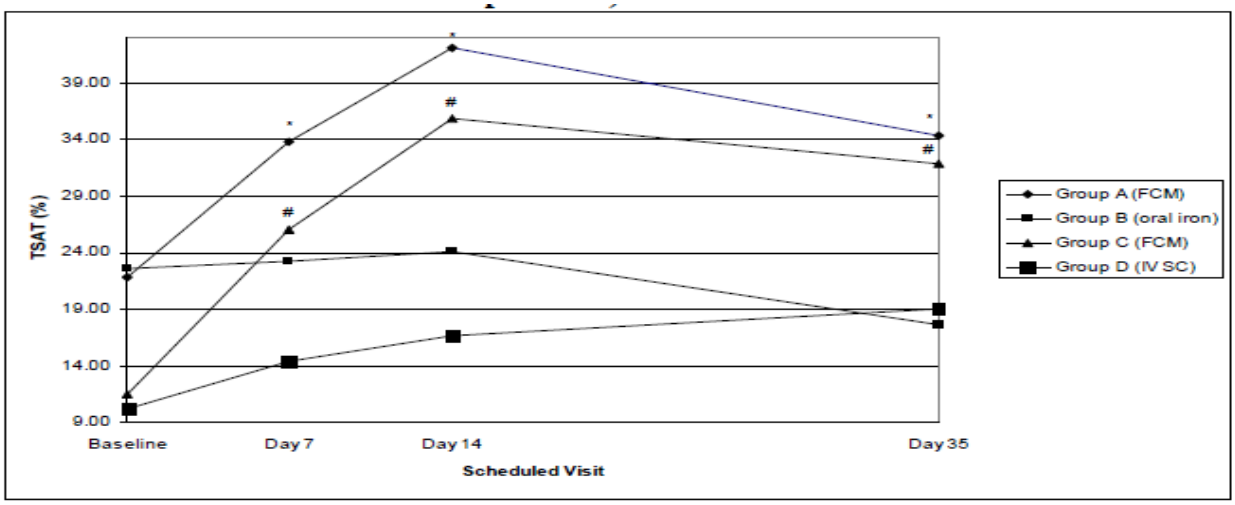
Sponsor's figure

Figure 3. Mean Ferritin Values at Each Scheduled Visit in Study 1VIT09031



Sponsor's figure

Figure 4. Mean TSAT Values at Each Scheduled Visit in Study 1VIT09031



Sponsor's figure

Study 1VIT09030

Hemoglobin increase ≥ 1.0 g/dL
Overall, the proportion of subjects with an increase in hemoglobin ≥1.0 g/dL anytime between baseline and Day 56 or time of intervention was similar between the FCM (48%) and the Venofer group (41%).

Mean changes in iron indices
The mean increases in ferritin and TSAT from baseline to each scheduled visit (including Day 7)

between baseline and Day 56 or time of intervention were greater in the FCM group than those observed in the Venofer group.

The results of these secondary efficacy endpoints are shown in the table below.

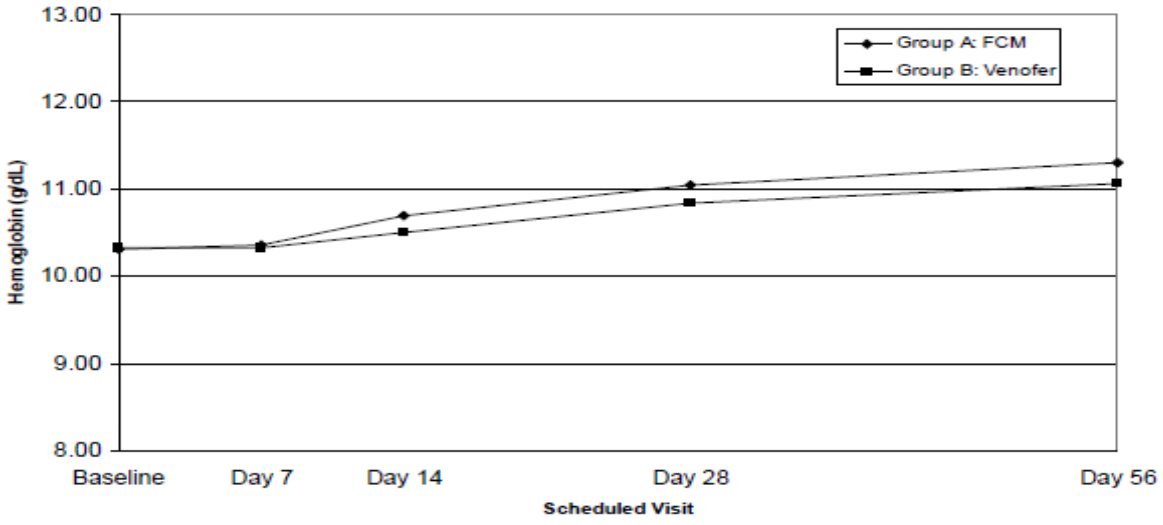
Table 16. Results of Secondary Efficacy Endpoints in Study 1VIT09030

Secondary Efficacy Endpoints	FCM	Venofer
Hemoglobin increase ≥1 g/dL	607/1249 (48.6%)	510/1244 (41.0%)
Mean change (SD) in Ferritin (ng/mL)	N=1249 734.7 (337.8)	N=1244 288.9 (169.8)
Mean change (SD) in TSAT (%)	N=1247 29.5 (17.0)	N=1243 16.3 (14.2)

Reviewer's table

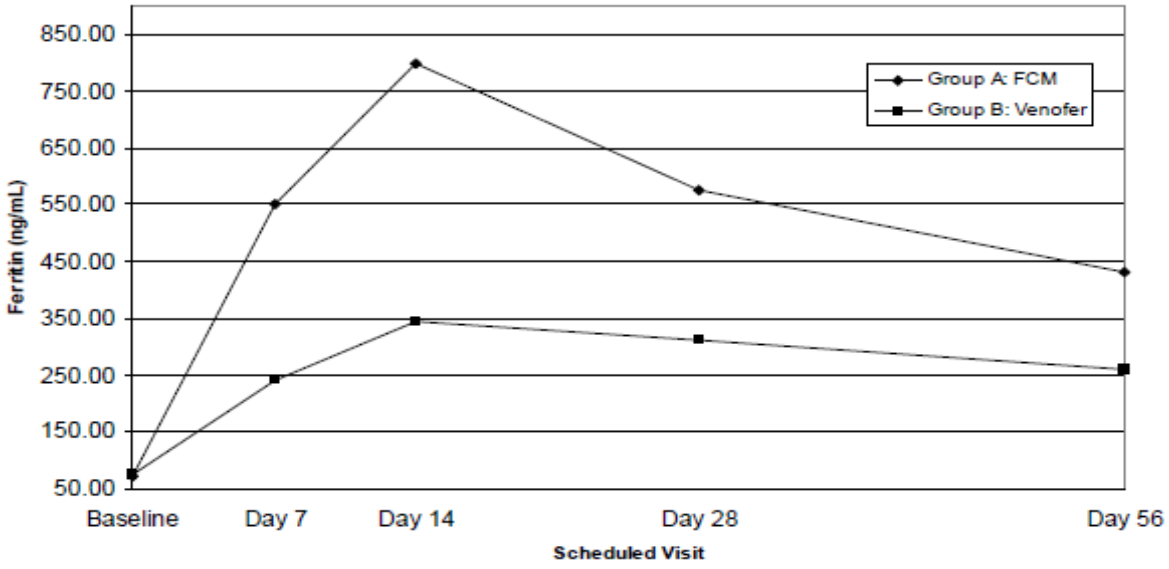
Mean changes in hemoglobin, ferritin and TSAT at each visit
Mean hemoglobin, ferritin, and TSAT values at each scheduled visit by treatment are presented in Figures below. Mean Ferritin and TSAT reached to the highest values at Day 14 and the mean hemoglobin level increased gradually over the time to the highest value at Day 56 for both treatment groups.

Figure 5. Mean Hemoglobin Values at Each Scheduled Visit in Study 1VIT09030



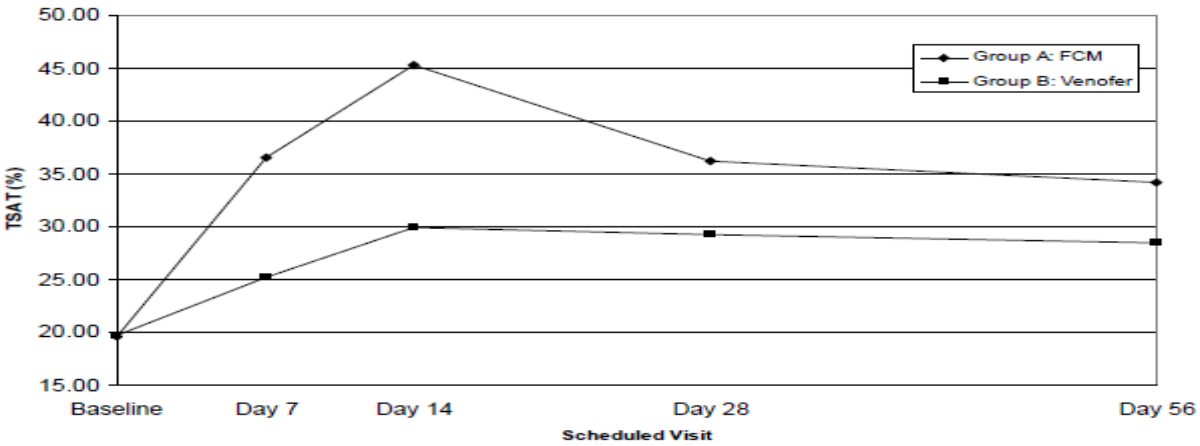
Sponsor's figure

Figure 6. Mean Ferritin Values at Each Scheduled Visit in Study 1VIT09030



Sponsor's figure

Figure 7. Mean TSAT Values at Each Scheduled Visit in Study 1VIT09030



Sponsor's digure

6.1.6 Other Endpoints

The results for other iron parameters including serum iron and TIBC were consistent with results from TSAT and ferritin level.

6.1.7 Subpopulations

Study 1VIT09031

The results of mean change in hemoglobin from baseline to day 35 or the time of intervention in subgroups by baseline hemoglobin category and the etiology of IDA were consistent with the primary efficacy analysis (see table below).

Table 17. Subgroup Analysis for Mean Changes in Hemoglobin in Study 1VIT09031

	Cohort 1		Cohort 2	
	FCM (N=244)	Oral Iron (N=251)	FCM (N=245)	IVSC (N=237)
Baseline Hemoglobin ≤ 9 g/dL				
Baseline				
n	23	23	117	116
Mean (SD)	8.70 (0.761)	9.12 (1.427)	7.81 (1.033)	7.83 (0.996)
Highest Value				
n	23	23	117	116
Mean (SD)	11.73 (1.452)	9.77 (1.589)	11.75 (1.320)	10.52 (1.219)
Change to Highest Value				
n	23	23	117	116
Mean (SD)	3.03 (1.587)	0.65 (0.723)	3.94 (1.370)	2.69 (1.256)
Baseline Hemoglobin 9.1-10 g/dL				
Baseline				
n	48	48	58	58
Mean (SD)	9.99 (0.637)	9.88 (0.622)	9.65 (0.564)	9.57 (0.446)
Highest Value				
n	48	48	58	58
Mean (SD)	11.80 (1.052)	10.71 (0.946)	12.09 (1.146)	11.44 (0.863)
Change to Highest Value				
n	48	48	58	58
Mean (SD)	1.82 (1.039)	0.83 (0.872)	2.44 (1.343)	1.87 (0.956)
Baseline Hemoglobin ≥ 10.1 g/dL				
Baseline				
n	173	180	70	63
Mean (SD)	11.02 (0.702)	11.01 (0.741)	10.88 (0.820)	10.69 (0.620)
Highest Value				
n	173	180	70	63
Mean (SD)	12.32 (1.044)	11.82 (0.873)	12.41 (0.990)	12.13 (0.874)
Change to Highest Value				
n	173	180	70	63
Mean (SD)	1.31 (1.013)	0.80 (0.790)	1.53 (0.984)	1.44 (1.038)

Etiology of IDA-HUB				
Baseline				
n	125	123	108	106
Mean (SD)	10.67 (1.092)	10.57 (1.000)	9.14 (1.889)	9.00 (1.644)
Highest Value				
n	125	123	108	106
Mean (SD)	12.27 (1.079)	11.51 (1.225)	12.16 (1.184)	10.99 (1.360)
Change to Highest Value				
n	125	123	108	106
Mean (SD)	1.60 (1.257)	0.94 (0.823)	3.02 (1.599)	1.99 (1.308)
Etiology of IDA-GI Disorders				
Baseline				
n	26	27	57	53
Mean (SD)	10.22 (0.855)	10.41 (0.937)	9.28 (1.329)	9.34 (1.270)
Highest Value				
n	26	27	57	53
Mean (SD)	11.98 (1.351)	10.95 (1.008)	11.99 (1.294)	11.30 (1.150)
Change to Highest Value				
n	26	27	57	53
Mean (SD)	1.76 (1.102)	0.54 (0.578)	2.71 (1.481)	1.96 (1.120)
Etiology of IDA-Other				
Baseline				
n	93	101	80	78
Mean (SD)	10.60 (0.912)	10.74 (1.091)	8.98 (1.328)	8.83 (1.300)
Highest Value				
n	93	101	80	78
Mean (SD)	12.07 (1.082)	11.43 (1.151)	11.85 (1.213)	11.34 (1.155)
Change to Highest Value				
n	93	101	80	78
Mean (SD)	1.48 (1.136)	0.68 (0.791)	2.87 (1.802)	2.52 (1.193)

SD-standard deviations
Reviewer's Table

The proportions of patients with hemoglobin >12 g/dL or hemaglobin >12 g/dl and an increase in ferritin >160 ng/mL from baseline to day 35 or the time of intervention were greater in the FCM group than in the oral iron or IV standard care groups in all subgroups by baseline hemoglobin category and the etiology of IDA (see tables below).

Table 18. Subgroup Analysis for Hemoglobin >12.0 g/dL in Study 1VIT09031

	Cohort 1		Cohort 2	
	FCM (N=244) n/N (%)	Oral Iron (N=251) n/N (%)	FCM (N=245) n/N(%)	IV SC (N=237) n/N (%)
Baseline Hemoglobin				
≤ 9.0 g/dL	9/23 (39.1%)	2/23 (8.7%)	49/117 (41.9%)	12/116 (10.3%)
9.1-10.0 g/dL	21/48 (43.8%)	5/48 (10.4%)	31158 (53.4%)	16/58 (27.6%)
≥10.1 g/dL	109/173 (63.0%)	66/180 (36.7%)	44/70 (62.9%)	30/63 (47.6%)

Etiology of IDA HUB GI disorders Other	 791125 (63.2%) 12/26 (46.2%) 48/93 (51.6%)	 36/123 (29.3%) 4/27 (14.8%) 33/101 (32.7%)	 64/108 (59.3%) 29/57 (50.9%) 31180 (38.8%)	 24/106 (22.6%) 13/53 (24.5%) 21/78 (26.9%)

Reviewer's Table

Table 19. Subgroup Analysis for Hemoglobin >12.0 g/dL and an Increase in Ferritin >160 ng/mL in Study 1VIT09031

	Cohort 1		Cohort2	
	FCM (N=244) n/N (%)	Oral Iron (N=251) n/N (%)	FCM (N=245) n/N(%)	IV SC (N=237) n/N (%)
Baseline Hemoglobin ≤ 9.0 g/dL 9.1-10.0 g/dL ≥10.1 g/dL	 8/23 (34.80%) 19/48 (39.6%) 106/173(61.3%)	 0/23 0/48 1/180 (0.6%)	 46/117 (39.3%) 29/58 (50.0%) 43/7 0 (61.4%)	 4/116 (3.4%) 4/58 (6.9%) 6/63 (9.5%)
Etiology of IDA HUB GI disorders Other	 76/125 (60.8%) 12/26 (46.2%) 45/93 (48.4%)	 1/123 (0.8%) 0/27 0/101	 61/108 (56.5%) 27/57 (47.4%) 30/80 (37.5%)	 6/106 (5.7%) 4/53 (7.5%) 4/78 (5.1%)

Reviewer's Table

The proportions of patients with clinically meaningful increase in hemoglobin (defined as ≥ 1 g/dL for CKD, ≥ 2 g/dL for HUB or GI disorders, ≥ 3 g/dL for postpartum, and ≥ 2 g/dL for others) anytime between baseline and day 35 or time of intervention were also greater in the FCM group than in the oral iron or IV standard care groups in all subgroups by baseline hemoglobin category and the etiology of IDA s (see table below).

Table 20. Subgroup Analysis for Clinically Meaningful Increase in Hemoglobin in Study 1VIT09031

	Cohort 1		Cohort 2	
	FCM (N=244) n/N (%)	Oral Iron (N=251) n/N (%)	FCM (N=245) n/N(%)	IV SC (N=237) n/N (%)
Baseline Hemoglobin ≤ 9.0 g/dL 9.1-10.0 g/dL ≥10.1 g/dL	 19/23 (82.6%) 20/48 (41.7%) 41/173 (23.7%)	 1/23 (4.3%) 6/48 (12.5%) 15/180 (8.3%)	 107/117 (91.5%) 36/58 (62.1%) 21/70 (30.0%)	 74/116 (63.8%) 25/58 (43.1%) 14/63 (22.2%)

Etiology of IDA HUB GI disorders Other	 43/125 (34.4%) 12/26 (46.2%) 25/93 (26.9%)	 12/123 (9.8%) 1/27 (3.7%) 9/101 (8.9%)	 78/108 (72.2%) 37/57 (64.9%) 49/80 (61.3%)	 48/106 (45.3%) 22/53 (41.5%) 43/78 (55.1%)

Reviewer's Table

Study 1VIT09030

When analyzed by baseline hemoglobin, use of EPO, and CKD stage, the mean increase in hemoglobin was numerically greater in the FCM group than that observed in the Venofer group for all subgroups and demonstrated noninferiority of FCM to Venofer for all comparisons.

Table 21. Subgroup Analysis for Mean Changes in Hemoglobin in Study 1VIT09030

	FCM			Venofer		
	Baseline	Highest	Change to Highest	Baseline	Highest	Change to Highest
Baseline Hemoglobin ≤:9.0 g/dL n Mean (SD)	 100 8.43 (0.52)	 100 10.13 (1.68)	 100 1.70 (1.65)	 96 8.48 (0.57)	 96 9.92 (1.25)	 96 1.43 (1.25)
Baseline Hemoglobin 9.1-10.0 g/dL n Mean (SD)	 280 9.60 (0.29)	 280 10.89 (1.13)	 280 1.29 (1.12)	 279 9.60 (0.31)	 279 10.74 (1.05)	 279 1.14 (1.01)
Baseline Hemoglobin ≥ 10.1 g/dL n Mean (SD)	 869 10.75 (0.41)	 869 11.76 (0.95)	 869 1.01 (0.89)	 869 10.76 (0.42)	 869 11.56 (0.87)	 869 0.80 (0.80)
No EPO Use n Mean (SD)	 1024 10.32 (0.823)	 1024 11.43 (1.15)	 1024 1.11 (1.01)	 1034 10.34 (0.81)	 1034 11.27 (1.06)	 1034 0.93 (0.93)
Use of EPO n Mean (SD)	 225 10.27 (0.87)	 225 11.47 (1.35)	 225 1.21 (1.17)	 210 10.24 (0.89)	 210 11.15 (1.17)	 210 0.90 (0.87)
CKD Stage 2 n Mean (SD)	 68 10.41 (0.78)	 68 12.04 (1.27)	 68 1.63 (1.35)	 77 10.53 (0.91)	 77 11.96 (1.10)	 77 1.43 (1.12)
CKD Stage 3-4 n Mean (SD	 1091 10.33 (0.82)	 1091 11.45 (1.15)	 1091 1.13 (1.02)	 1067 10.35 (0.80)	 1067 11.25 (1.03)	 1067 0.91 (0.89)
CKD Stage 5 n Mean (SD)	 90 10.02 (0.92)	 90 10.78 (1.27)	 90 0.76 (0.96)	 100 9.94 (0.93)	 100 10.63 (1.24)	 100 0.69 (0.94)

SD=standard deviation
Reviewer's Table

The subgroup analysis for increase in hemoglobin ≥ 1.0 g /dl from baseline also showed numerically more responders in the FCM group as compared to the Venofer group except in subjects with CKD stage 5 (see Table below).

Table 22. Subgroup Analysis for Hemoglobin ≥ 1.0 g/dL in Study 1VIT09030

	FCM (N=1249) n/N(%)	Venofer (N=1244) n/N(%)
Baseline Hemoglobin		
≤9.0 g/dL	63/100 (63.0%)	57/96 (59.4%)
9.1-10.0 g/dL	152/280 (54.3%)	144/279 (51.6%)
≥10.1 g/dL	392/869 (45.1%)	309/869 (35.6%)
Use of EPO		
No	491/1024 (48.0%)	411/1034 (39.8%)
Yes	116/225 (51.6%).	99/210 (47.1%)
CKD Stage		
2	43/68 (63.2%)	41/77 (53.3%)
3-4	533/1091 (48.9%)	433/1067 (40.6%)
5	31/90 (34.4%)	36/100 (36.0%)

Reviewer's Table

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The proposed dosing regimen of 15 mg/kg with the maximum single dose of 750 mg and the maximum cumulative dose of 1500 mg was studied in the two pivotal clinical trials. A high maximum single dose of 1000 mg with a high maximum cumulative dose of 2500 mg was studied in clinical trials for previous (NDA 22-054) submission that showed a mortality disadvantage of Injectafer as compared to oral iron.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No specific studies were conducted to evaluate the tolerance effect. In Study 1VIT09031, the mean increase in hemoglobin, TSAT and ferrtin in the FCM group remained numerically greater at Day 35 as compared to those in the oral iron and IV standard care groups.

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

A total of 1775 subjects have received the proposed Injectafer dosing regimen of 15mg/kg with the maximum of single dose of 750 mg and maximum total dose of 1500 mg in two pivotal clinical studies. The majority of patients have received 750 mg dose for 2 doses. A total of 2566 subjects have been exposed to Injectafer as a maximum single dose of 750 mg with the different total doses. A total of 6679 subjects have been exposed to Injectafer with different dosing regimens in the Phase 2/3 development program.

The mortality rates were similar between Injectafer for the proposed dosing regimen and the comparators in pooled analysis of the two pivotal studies (16/1775, 0.9% vs. 21/1783, 1.2%) and were also similar between Injectafer with the maximum single dose of 750 mg with the different total doses and the comparator in pooled analysis of the five studies (17/2566, 0.7% vs. 22/2590, 0.8%). For all completed studies, the overall mortality rate was 0.5% (33/6679) in the Injectafer-treated patients and 0.6% (30/5394) in comparator-treated patients.

In the two pivotal trials, no significant difference was found for the pre-specified primary cardiovascular composite safety endpoint (including death, MI, stroke, unstable angina, CHF, hypertension and hypotension) between Injectafer and Venofer or pooled comparators (10.8%, 11.1%, and 9.7%, respectively). Hypertensive events were found to be significantly higher in the Injectafer group as compared to the Venofer group, or the pooled comparator group (6.0%, 4.1%, and 3.5%, respectively).

In the pooled analysis of the two pivotal trials, the overall incidence of treatment-emergent serious adverse events was 12.8% in the Injectafer group, 14.0% in the Venofer group, and 12.5% in the pooled comparators group. The most common treatment-emergent serious adverse events in the Injectafer group were cardiac failure congestive (1.7%) and pneumonia (1.0%), which were similar to values in the pooled comparators and Venofer groups. The incidence of treatment-emergent adverse events resulting in premature discontinuation of study drug was 2.9% in the Injectafer group, 2.3% in the Venofer group, and 2.1% in the pooled comparators group. The most common treatment-emergent adverse events resulting in premature discontinuation of study drug in the Injectafer group were flushing and hypertension (0.5% and 0.6%, respectively).

The incidence of treatment-emergent serious or severe hypersensitivity/allergic reactions was 1.5% in the Injectafer group, 1.6% in the Venofer group, and 1.5% in the pooled comparators group in the two pivotal trials.

In the pooled analysis of the two clinical trials, 60.3% of subjects in the FCM group experienced at least one treatment-emergent adverse event as compared to 59.0% of subjects in the Venofer group, and 55.2% of subjects in the pooled comparator group. The most common (≥2.0%) treatment-emergent adverse events in the FCM group were nausea (11.4%), hypertension (8.6%), dizziness (4.3%), flushing (3.4%), headache (3.3%), vomiting (3.3%), diarrhea (3.2%), urinary tract infection (3.2%), hypotension (2.8%), hypophosphatemia (2.7%), constipation (2.3%), fatigue (2.3%), back pain (2.3%), peripheral edema (2.3%), and congestive heart failure (2.1%). Adverse events that occurred more frequently (by ≥1%) with Injectafer than with pooled

comparator were nausea, hypertension, flushing, vomiting, hypophosphatemia, back pain, hyperkalemia, ALT increased, injection site discoloration, and hot flush.

The incidence of any drug-related treatment-emergent adverse event was greater in the FCM group (23.5%) compared with the Venofer (17.3%) and pooled comparators (15.9%) group. The most common (≥1.0%) drug-related treatment-emergent adverse events in the FCM group were nausea (7.2%), hypertension (3.8%), flushing (2.7%), hypophosphatemia (2.1%), dizziness (2.0%), vomiting (1.7%), injection site discoloration (1.4%), headache (1.2%), ALT increased (1.1%), and dysgesusia (1.1%). Adverse events that occurred more frequently (by ≥1%) with Injectafer than with pooled comparator included nausea, hypertension, flushing, hypophosphatemia, vomiting, and injection site discoloration.

In conclusion, Injectafer has demonstrated similar safety profiles as Venofer for mortality, cardiovascular events, serious adverse events, and overall adverse events. Injectafer-treated patients experienced more hypertensive events, flushing and hypophosphatemia.

Safety evaluation and results are presented in detail below.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

See Section 5.1 Tables 2 and 3 for all studies used to evaluate the safety.

7.1.2 Categorization of Adverse Events

MedDRA terminology was used to classify all adverse events with respect to SOC and preferred term in clinical trials. In addition, a composite cardiovascular endpoint was assessed in two pivotal trials. See Section 7.3.4 for components and definitions of the composite endpoint.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Overall mortality and other safety data was analyzed for different datasets of pooled studies: primary maximum 750 mg FCM infusion (2 studies), all maximum 750 mg FCM infusion studies (5 studies), Phase 2/3 short-term IDA and CHF studies (20 studies), other short-term active-controlled IDA studies with maximum FCM doses other than 750 mg (10 studies), and CHF studies (3 studies). The primary maximum 750 mg FCM infusion studies included two pivotal trials and were used as the primary support for the proposed dosing regimen. All maximum 750 mg FCM infusion studies were used as the secondary support for the proposed maximum single dose of 750 mg of FCM. See table below for individual studies included in each dataset.

Table 23. Safety Analysis Pooling Datasets

Analysis Dataset	Study Population: Studies
Primary Maximum 750 mg FCM Infusion Studies: 2 trials	IDA: 1VIT09031 NDD-CKD: 1VIT09030
All Maximum 750 mg FCM Infusion Studies: 5 trials	IDA: 1VIT09031, 1VIT08021, 1VIT08020, 1VIT08019 NDD-CKD: 1VIT09030
Other Short-Term Active-Controlled IDA Studies with Maximum FCM Doses Other than 750 mg: 10 trials	Postpartum: 1VIT06011, 1VIT03001, VIT-IV-CL-009 HUB: 1VIT04002/1VIT04003 Postpartum/HUB: 1VIT07017 NDD-CKD: 1VIT04004 HD-CKD: VIT-IV-CL-015 NDD- and HD-CKD: 1VIT07018 GI: VIT-IV-CL-008, FER-IBD-COR
Chronic Heart Failure Studies: 3 trials	CHF: FER-CARS-01, FER-CARS-02, and FER-CARS-03
Phase 2/3 Short-Term IDA and CHF Studies: 20 trials	IDA: 1VIT09031, 1VIT08021, 1VIT08020, 1VIT08019 NDD-CKD: 1VIT09030, 1VIT04004 HD-CKD: VIT-IV-CL-015, VIT-53214 NDD- and HD-CKD: 1VIT07018 Postpartum: 1VIT06011, 1VIT03001, VIT-IV-CL-009 HUB: 1VIT04002/1VIT04003 Postpartum/HUB: 1VIT07017 GI: VIT-IV-CL-003, VIT-IV-CL-008, FER-IBD-COR CHF: FER-CARS-01, FER-CARS-02, FER-CARS-03

Note: Analys1s sets are not mutually exclusive.
IDA=iron-deficiency anemia; NDD=non-dialysis dependent; CKD=chronic kidney disease;
HUB=heavy uterine bleeding; HD=hemodialysis dependent; GI=gastrointestinal; CHF=chronic heart failure
Reviewer's table

7.2 Adequacy of Safety Assessments

The safety assessments are adequate.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Primary Maximum 750 mg FCM Infusion Studies

Among the 1775 subjects treated with FCM in the primary maximum 750 mg FCM infusion studies, the majority (96.0%) received 2 doses of FCM (see Table below). The mean maximum single dose was 745.2 (± 46.1) mg and the mean total dose of FCM was 1455.9 (± 176.2) mg.

Table 24. Extent of Exposure in Primary Maximum 750 mg FCM Infusion Studies

	FCM (N=1775)
Number of Infusions	
1	70 (3.9%)
2	1704 (96.0%)
3	1 (0.1%)
Total Dose of Iron (mg) Received	
Mean (SD)	1455.9 (176.16)
Median	1500
Minimum, Maximum	25.0, 1750.0
Maximum Single Dose (mg)	
Mean (SD)	745.2 (46.06)
Median	750
Minimum, Maximum	25.0, 1000.0

SD=standard deviation
Reviewer's table

All Maximum 750 mg FCM Infusion(s) Studies

Among the 2566 subjects treated with FCM in all maximum 750 mg FCM studies, the number of infusions received ranged from 1 to 4; the majority of the subjects received 2 doses (74.9%) or 1 dose (17.8%) of FCM. The mean total dose of FCM received was 1358.9 (± 327.19) mg and the mean maximum single dose received was 745.3 (± 43.74) mg (see Table below).

Table 25. Extent of Exposure in All Maximum 750 mg FCM Infusion Studies

	FCM (N=2566)
Number of Infusions	
1	457 (17.8%)
2	1922 (74.9%)
3	186 (7.2%)
4	1(<0.1%)
Total Dose of Iron (mg) Received	
Mean (SD)	1358.9 (327.19)
Median	1500
Minimum, Maximum	12.5, 2250.0
Maximum Single Dose (mg)	
Mean (SD)	745.3 (43.74)
Median	750
Minimum, Maximum	12.5, 1000.0

SD=standard deviation
Reviewer's table

Phase 2/3 Short-Term IDA and CHF Studies

Among the 5799 subjects treated with FCM in the Phase 2/3 short-term IDA and CHF studies, the number of infusions received ranged from 1 to 14. The majority of the subjects

received 2 doses (50.9%) or only 1 dose (32.4%) of FCM. The mean total dose of FCM received was 1301.5 (± 393.17) mg and the mean maximum single dose received was 781.7 (± 278.15) mg (see Table below).

Table 26. Extent of Exposure in All Phase 2/3 Short-Term IDA and CHF Studies

	FCM (N=5799)
Number of Infusions	
1a	1881 (32.4%)
2	2951 (50.9%)
3	349 (6.0%)
4	20 (0.3%)
5	32 (0.6%)
6	104 (1.8%)
7	94 (1.6%)
8	68 (1.2%)
9	70 (1.2%)
10	127 (2.2%)
11	86 (1.5%)
12	11 (0.2%)
14	1(<0.1%)
Total Dose of Iron (mg) Received	(N=5794)
Mean (SD)	1301.5 (393.17)
Median	1400
Minimum, Maximum	0.0, 3400.0
Maximum Single Dose (mg)	(N=5794)
Mean(SD)	781.7 (278.15)
Median	750
Minimum, Maximum	0.0, 3000.0

SD=standard deviation
Note: 5 subjects from Study FER-CARS-02 never received study drug due to adverse events, but are included in the Safety Population.
a Subjects with 0 mg total dose are listed under the 1 infusion category.
Reviewer's table

7.2.2 Explorations for Dose Response

Dose response was not explored in studies. However, high single dose with high total dose was studied in previous clinical trials submitted in NDA 22-054.

7.2.3 Special Animal and/or In Vitro Testing

See Section 4.3 for information.

7.2.4 Routine Clinical Testing

Routine clinical testing of clinical trials is adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

See Section 4.4 for available pharmacodynamic and pharmacokinetic information. No interaction studies were performed.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Hypersensitivity reactions are a known risk associated with the use of IV iron products for the treatment of iron deficiency anemia. Hypersensitivity reactions were evaluated in the Injectafer clinical trials.

7.3 Major Safety Results

7.3.1 Deaths

Mortality was analyzed for different datasets of pooled studies: primary maximum 750 mg FCM infusion (2 studies), all maximum 750 mg FCM infusion studies (5 studies), other short-term active-controlled IDA studies with maximum FCM doses other than 750 mg (10 studies), CHF studies (3 studies), phase 2/3 short-term IDA and CHF studies (20 studies). See Section 7.1.3 for listed studies included in each analysis dataset.

Four Phase 2/3 studies are not pooled with other studies. They were placebo-controlled single-dose crossover study 1VIT05006, uncontrolled 44-week Study 1VIT05005 (extension to Study 1VIT04004), placebo-controlled 8-month Study FER-IBD-MAIN (extension to Study FER-IBD-COR), and 1VIT05009 (subjects with restless legs syndrome).

The following table summaries the mortality rate in the different pooled datasets and all completed phase 2/3 studies. No significant difference in mortality rate was observed between the FCM group and the pooled comparators in these analyses. The mortality rate was numerically lower in the FCM group as compared to comparator except in the other short-term active-controlled IDA studies with maximum FCM doses other than 750 mg dataset. In this dataset, all subjects in the FCM group had received the higher FCM dose of maximum single dose of 1000 mg and maximum cumulative dose of 2500 mg except those undergoing hemodialysis in the HD-CKD study. The overall mortality rate between the FCM group and the comparator was similar when all subjects were included in all completed phase 2/3 studies (0.5% and 0.6%, respectively).

Table 27. Deaths in Phase 2/3 Clinical Program by Analysis Dataset

Analysis Set	FCM n/N (%)	Pooled Comparators n/N (%)
Primary Maximum 750 mg FCM Infusion Studies	16/1775 (0.9%)	21/1783 (1.2%)
All Maximum 750 mg Infusion(s) Studies	17/2566 (0.7%)	22/2590 (0.8%)

Other Short-Term IDA, Active-Controlled IDA Studies with Maximum FCM Doses Other than 750 mg	5/2716 (0.2%)	2/2472 (0.1%)
CHF Studies	6/355 (1.7%)	6/210 (2.9%)
Phase 2/3 Short-Term IDA and CHF Studies	30/5799 (0.5%)	30/5272 (0.6%)
Phase 2/3 Studies Not Pooled*	3/880 (0.3%)	0/122 (0.0%)
All Completed Phase 2/3 Studies	33/6679 (0.5%)	30/5394 (0.6%)

Note: Analysis sets are not mutually exclusive.
*Include crossover study 1VIT05006, uncontrolled study 1VIT05005, placebo-controlled study FER-IBD-MAIN, and placebo-controlled study 1VIT05009 (RLS).
Reviewer's Table

The following table shows deaths that occurred in each individual studies and in combined all randomized controlled trials. In two pivotal studies (1VIT09030 and 1VIT09031), the mortality rate was similar between the FCM and the comparator. The sample size was relatively small with few deaths in other studies. The overall mortality rate in the FCM group was similar between the FCM group and the comparator when combining all randomized controlled studies (0.5% and 0.6%, respectively).

Table 28. Deaths in Completed Individual Studies

	FCM n/N (%)	Comparator n/N (%)
Primary Maximum 750 mg FCM Infusion Studies		
1VIT09030 (IDA)	15/1276 (1.2%)	18/1285 (1.4%)
1VIT09031 (NDD-CKD)	1/499 (0.2%)	3/498 (0.6%)
Other Maximum 750 mg FCM Infusion Studies		
1VIT08021 (IDA)	0/366	1/369 (0.3%)
1VIT08020 (IDA)	1/82 (1.2%)	0/78
Other Studies		
1VIT03001 (postpartum)	1/174 (0.6%)	0/178
1VIT04004 (NDD-CKD)	2/147 (1.4%)	0/103
1VIT07018 (CKD)	0/254	2/259 (0.8%)
VII-IV-CL-008 (IBD)	1/137 (0.7%)	0/63
VII-IV-CL-015 (HD-CKD)	1/119 (0.8%)	0/118
FER-CARS-01 (CHF)	0/30	1/42 (2.4%)
FER-CARS-02 (CHF)	5/304 (1.6%)	4/155 (2.6%)
FER-CARS-03 (CHF)	1/20 (5.0%)	1/14 (7.1%)
Controlled Trials Total	**28/5830 (0.5%)**	**30/5394 (0.6%)**
Uncontrolled Trials*	**5/849 (0.6%)**	**--**
Total	**33/6679 (0.5%)**	**30/5394 (0.6%)**

* Includes Studies 1VIT53214, 1VIT05005 and 1VIT05006
Reviewer's Table

The following table shows the deaths in the FCM group and in each comparator group in the three main datasets. The mortality rates in all three datasets were numerically lower in the FCM

group as compared to the Venofer group. The mortality rate was slightly higher in the FCM group as compared to the oral iron group (0.9% and 0.8%, respectively) in the primary maximum 750 mg infusion studies. Note that subjects in the FCM group included both CKD patients from 1VIT09030 and non-CKD patients in 1VIT09031 and all subjects in the oral iron group were non-CKD patients from 1VIT09031. In Study 1VIT09031, in Cohort 1 in randomized non-CKD subjects with inadequate response to oral iron, there was no death in the FCM group as compared to 2 deaths in the oral iron group (0.79%).

Table 29. Deaths by Treatment Group in Three Main Datasets

Analysis set	FCM	Oral Iron	Any IV Iron	Venofer	Other Comparators
Primary Maximum 750 mg FCM Infusion Studies	16/1775 (0.9%)	2/253 (0.8%)	19/1530 (1.2%)	19/1503 (1.3%)	-
All Maximum 750 mg FCM Infusion(s) Studies	17/2566 (0.7%)	3/666 (0.5%)	19/1880 (1.0%)	19/1678 (1.1%)	0/44
Phase 2/3 Short-Term IDA and CHF Studies	30/5799 (0.5%)	3/2497 (0.1%)	22/2439 (0.9%)	21/2196 (1.0%)	5/336 (1.5%)

Reviewer's Table

Primary Maximum 750 mg FCM Infusion Studies

In the primary maximum 750 mg FCM infusion studies, 16 (0.9%) subjects in the FCM group and 21 (1.2%) subjects in the pooled comparators group experienced at least 1 adverse event that resulted in death. Of the 16 deaths in the FCM group, 2 occurred < 7 days after the last dose of study drug, none occurred between 7 and 30 days after the last dose of study drug, 6 occurred between 30 and 60 days after the last dose of study drug, 5 occurred between 60 and 90 days after the last dose of study drug, and 3 occurred >90 days after the last dose of study drug. There was no significant difference in the distribution of deaths across time as compared to the Venofer and pooled comparators groups.

None of the deaths were considered related to study drug, except for 1 death due to arrhythmia that occurred in an FCM subject in Study 1VIT09030 that was considered possibly related to study drug by investigator.

The possibly drug-related death occurred in an 86-year-old Caucasian male with a history of diastolic dysfunction, bradycardia, supraventricular tachycardia with cardiac ablation, grade II/IV systolic murmur, pulmonary hypertension, chronic obstructive pulmonary disease, diabetes, hypertension, hyperlipidemia, hyperkalemia, hypothyroidism, diverticular disease, pneumonia, organic brain syndrome, anemia, depression, and impaired renal function. Concomitant medications included amiodarone. On Day 0, he was randomized and received a 750 mg injection of FCM. On Day (b) (6) he received the second and last injection of FCM for a total cumulative dose of 1500 mg. On Day (b) (6) he was found

unresponsive on his couch at home and died the same day. The presumed cause of death was cardiac arrhythmia. An autopsy was not performed. In the Investigator's opinion, the fatal event of cardiac arrhythmia was possibly related to FCM. No detailed clinical information was available prior to death to evaluate the cause of the death in this patient.

A summary of treatment-emergent adverse events that resulted in death in the primary maximum 750 mg infusion studies is presented in the following table. No differences were found in the frequency of these adverse events between the FCM and the other treatment groups.

Table 30. Treatment-Emergent Adverse Events Resulting in Death in Primary Maximum 750mg FCM Infusion Studies

Preferred Term	FCM (N=1775)	Pooled Comparators[a] (N=1783)	Oral Iron (N=253)	Venofer (N=1503)
At Least 1 Adverse Event* Resulting in Death	16 (0.9%)	21 (1.2%)	2 (0.8%)	19 (1.3%)
Cardiac failure congestive	2 (0.1%)	4 (0.2%)	0	4 (0.3%)
Cardio-respiratory arrest	2 (0.1%)	3 (0.2%)	0	3 (0.2%)
Pneumonia	2 (0.1%)	1 (0.1%)	0	1 (0.1%)
Chronic obstructive pulmonary disease	2 (0.1%)	0	0	0
Acute myocardial infarction	1 (0.1%)	1 (0.1%)	0	1 (0.1%)
Arrhythmia	1 (0.1%)	1 (0.1%)	0	1 (0.1%)
Atrial fibrillation	1 (0.1%)	0	0	0
Sepsis	1 (0.1%)	1 (0.1%)	0	1 (0.1%)
Dehydration	1 (0.1%)	0	0	0
Lung neoplasm malignant	1 (0.1%)	0	0	0
Metastatic renal cell carcinoma	1 (0.1%)	0	0	0
Cerebrovascular accident	1 (0.1%)	0	0	0
Renal failure	1 (0.1%)	1 (0.1%)	0	1 (0.1%)
Renal failure acute	1 (0.1%)	0	0	0
Aortic dissection	1 (0.1%)	0	0	0
Cardiac arrest	0	2 (0.1%)	0	2(0.1%)
Cardiogenic shock	0	1 (0.1%)	0	1 (0.1%)
Myocardial infarction	0	1 (0.1%)	0	1 (0.1%)
Death	0	1 (0.1%)	1 (0.4%)	0
Sudden cardiac death	0	1 (0.1%)	0	1 (0.1%)
Pneumonia streptococcal	0	1(0.1%)	0	1 (0.1%)
Septic shock	0	1 (0.1%)	1 (0.4%)	0
Accidental overdose	0	1 (0.1%)	0	1 (0.1%)
Head injury	0	1 (0.1%)	0	1 (0.1%)
Pulmonary fibrosis	0	1 (0.1%)	0	1 (0.1%)
Respiratory failure	0	1 (0.1%)	0	1 (0.1%)

a Includes oral iron, Venofer, and other forms of IV iron.
* Patients may experience more than one adverse event
Reviewer's table

All Maximum 750 mg FCM Infusion(s) Studies

A summary of treatment-emergent adverse events that resulted in death in the all maximum

750 mg FCM infusion(s) studies is presented in Table below. There were no deaths in 44 subjects who received placebo. There were also no differences in the frequency of these adverse events between the FCM and other treatment groups.

Table 31. Treatment-Emergent Adverse Events Resulting in Death in All Maximum 750mg FCM Infusion Studies

Preferred Term	FCM (N=2566)	Pooled Comparators* (N=2590)	Oral Iron (N=666)	Any IV Iron (N=1880)	Venofer (N=1678)
At Least 1 Adverse Event** Resulting in Death	17(0.7%)	22 (0.8%)	3 (0.5%)	19 (1.0%)	19(1.1%)
Cardiac failure congestive	2(0.1%)	4 (0.2%)	0	4 (0.2%)	4 (0.2%)
Cardio-respiratory arrest	2(0.1%)	3 (0.1%)	0	3 (0.2%)	3 (0.2%)
Pneumonia	2(0.1%)	2 (0.1%)	1 (0.2%)	1 (0.1%)	1 (0.1%)
Chronic obstructive pulmonary disease	2(0.1%)	0	0	0	0
Acute myocardial infarction	1(<0.1%)	1 (<0.1%)	0	1 (0.1%)	1 (0.1%)
Arrhythmia	1(<0.1%)	1(<0.1%)	0	1 (0.1%)	1 (0.1%)
Atrial fibrillation	1(<0.1%)	0	0	0	0
Death (unspecified)	1(<0.1%)	1(<0.1%)	1 (0.2%)	0	0
Sepsis	1(<0.1%)	1 (<0.1%)	0	1 (0.1%)	1 (0.1%)
Dehydration	1(<0.1%)	0	0	0	0
Lung neoplasm malignant	1(<0.1%)	0	0	0	0
Metastatic renal cell carcinoma	1(<0.1%)	0	0	0	0
Cerebrovascular accident	1(<0.1%)	0	0	0	0
Renal failure	1(<0.1%)	1 (<0.1%)	0	1 (0.1%)	1 (0.1%)
Renal failure acute	1(<0.1%)	0	0	0	0
Aortic dissection	1(<0.1%)	0	0	0	0
Cardiac arrest	0	2 (0.1%)	0	2 (0.1%)	2 (0.1%)
Cardiogenic shock	0	1(<0.1%)	0	1 (0.1%)	1 (0.1%)
Myocardial infarction	0	1 (<0.1%)	0	1 (0.1%)	1 (0.1%)
Sudden cardiac death	0	1 (<0.1%)	0	1 (0.1%)	1 (0.1%)
Pneumonia streptococcal	0	1 (<0.1%)	0	1 (0.1%)	1 (0.1%)
Septic shock	0	1(<0.1%)	1 (0.2%)	0	0
Accidental overdose	0	1 (<0.1%)	0	1 (0.1%)	1 (0.1%)
Head injury	0	1(<0.1%)	0	1 (0.1%)	1 (0.1%)
Pulmonary fibrosis	0	1(<0.1%)	0	1 (0.1%)	1 (0.1%)
Respiratory failure	0	1(<0.1%)	0	1 (0.1%)	1 (0.1%)

* Includes oral iron, Venofer, other forms of IV iron and placebo.
** Patients may experience more than one adverse event
Reviewer's table

Phase 2/3 Short-Term IDA and CHF Studies

A summary of treatment-emergent adverse events that resulted in death in the Phase 2/3 short-term IDA and CHF studies is presented in Table below. It is noted that there were 4 sudden deaths in the FCM group as compared to 1 case in the pooled comparators group. All 4 cases occurred in patients with congestive heart disease in Study FER-CARS-02. In this study, for the FCM group, subjects received multiple doses of 200mg for an average total dose of 1,850 mg iron in the 24 week treatment period. In the study, 4 subjects treated with FCM and 3 subjects treated

with placebo died during the study period. All 7 death cases were reported as not related to study drug.

Table 32. Treatment-Emergent Adverse Events Resulting in Death in Phase 2/3 Short-Term IDA and CHF Studies

Preferred Term	FCM (N=5799)	Pooled Comparators (N=5272)	Oral Iron (N=2497)	Any IV Iron (N=2439)	Venofer (N=2196)	Other Comparators (N=336)
At Least 1 Adverse Event** Resulting in Death	30 (0.5%)	30 (0.6%)	3(0.1%)	22 (0.9%)	21 (1.0%)	5 (1.5%)
Sudden death	4 (0.1%)	1(<0.1%)	0	0	0	1 (0.3%)
Cardio-respiratory arrest	3 (0.1%)	3 (0.1%)	0	3 (0.1%)	3 (0.1%)	0
Cardiac failure congestive	2(<0.1%)	4 (0.1%)	0	4 (0.2%)	4 (0.2%)	0
Pneumonia	2 (<0.1%)	2 (<0.1%)	1(<0.1%)	1 (<0.1%)	1(<0.1%)	0
Sepsis	2 (<0.1%)	1 (<0.1%)	0	1 (<0.1%)	1(<0.1%)	0
Chronic obstructive pulmonary disease	2 (<0.1%)	0	0	0	0	0
Acute myocardial infarction	1(<0.1%)	1 (<0.1%)	0	1 (<0.1%)	1(<0.1%)	0
Arrhythmia	1(<0.1%)	1 (<0.1%)	0	1 (<0.1%)	1(<0.1%)	0
Atrial fibrillation	1 (<0.1%)	0	0	0	0	0
Cardiac arrest	1(<0.1%)	2 (<0.1%)	0	2 (0.1%)	2 (0.1%)	0
Cardiac failure	1(<0.1%)	1 (<0.1%)	0	1 (<0.1%)	1(<0.1%)	0
Myocardial infarction	1(<0.1%)	3 (0.1%)	0	2 (0.1%)	2 (0.1%)	1 (0.3%)
Death (unspecified)	1(<0.1%)	1 (<0.1%)	1(<0.1%)	0	0	0
Pulmonary tuberculosis	1 (<0.1%)	0	0	0	0	0
Polytraumatism	1(<0.1%)	0	0	0	0	0
Dehydration	1(<0.1%)	0	0	0	0	0
Lung neoplasm malignant	1(<0.1%)	0	0	0	0	0
Metatstatic renal cell carcinoma	1(<0.1%)	0	0	0	0	0
Cerebrovascular accident	1 (<0.1%)	0	0	0	0	0
Ischaemic stroke	1(<0.1%)	0	0	0	0	0
Peripartum cardiomyopathy	1(<0.1%)	0	0	0	0	0
Renal failure	1(<0.1%)	1(<0.1%)	0	1 (<0.1%)	1(<0.1%)	0
Renal failure acute	1(<0.1%)	0	0	0	0	0
Aortic dissection	1(<0.1%)	0	0	0	0	0
Cardiogenic shock	0	2(<0.1%)	0	1 (<0.1%)	1(<0.1%)	1 (0.3%)
Ventricular fibrillation	0	2(<0.1%)	0	1 (<0.1%)	0	1 (0.3%)

* Includes oral iron, Venofer, other forms of IV iron and placebo.
** Patients may experience more than one adverse event
Reviewer's table

7.3.2 Nonfatal Serious Adverse Events

Primary Maximum 750 mg FCM Infusion Studies

In the primary maximum 750 mg FCM infusion studies, the overall incidence of treatment-emergent serious adverse events was 12.8% in the FCM group, 14.0% in the Venofer group, and 12.5% in the pooled comparators group.

The most common treatment-emergent serious adverse events in the FCM group were cardiac failure congestive (1.7%) and pneumonia (1.0%), which were similar to the pooled comparators and Venofer groups. There were slightly more patients in the FCM group who experienced anemia and urinary tract infection as serious adverse events as compared to pooled comparator and the Venofer group.

A summary of treatment-emergent serious adverse events experienced by ≥ 0.5% of subjects in the FCM group in the primary maximum 750 mg FCM infusion studies is presented in the table below.

Table 33. Treatment-Emergent Serious Adverse Events Experienced by ≥ 0.5% of Subjects in Primary Maximum 750 mg FCM Infusion Studies

Preferred Term	FCM (N=l775)	Pooled Comparators (N=1783)	Oral Iron (N=253)	Venofer (N=1503)
At Least 1 SAEs	227 (12.8%)	223 (12.5%)	10 (4.0%)	211 (14.0%)
Cardiac failure congestive	30 (1.7%)	29 (1.6%)	0	29 (1.9%)
Pneumonia	17 (1.0%)	16 (0.9%)	0	16(1.1%)
Anemia	17 (1.0%)	5 (0.3%)	0	5 (0.3%)
Renal failure acute	13 (0.7%)	13 (0.7%)	1 (0.4%)	12 (0.8%)
Gastrointestinal hemorrhage	10 (0.6%)	10 (0.6%)	0	10 (0.7%)
Cellulitis	10 (0.6%)	6 (0.3%)	0	6 (0.4%)
Urinary tract infection	10 (0.6%)	2(0.1%)	0	2(0.1%)
Renal failure chronic	10 (0.6%)	10 (0.6%)	0	10 (0.7%)
Chronic obstructive pulmonary disease	9 (0.5%)	7 (0.4%)	0	7 (0.5%)

Reviewer's Table

The percentage of subjects who had a treatment-emergent serious adverse event considered related to study drug was 0.3% in the FCM and pooled comparators groups and 0.4% in the Venofer group. Treatment-emergent serious adverse events considered related to study drug in the FCM group were arrhythmia, supraventricular tachycardia, anaphylactoid reaction, hypersensitivity, and liver function test abnormal (1 subject each, 0.1%).

All Maximum 750 mg FCM Infusion(s) Studies

In all maximum 750 mg FCM infusion studies, the overall incidence of treatment-emergent serious adverse events was 9.9% in the FCM group, 12.1% in the any IV iron group, and 9.5% in the pooled comparators group.

The most common treatment-emergent serious adverse event in the FCM group was also cardiac failure congestive (1.2%) which was similar to the rate in the pooled comparators and the Venofer groups.

A summary of treatment-emergent serious adverse events experienced by ≥0.5% of subjects in the FCM group in all maximum 750 mg FCM infusion studies is presented in the following table.

Table 34. Treatment-Emergent Serious Adverse Events Experienced by ≥ 0.5% of Subjects in All Maximum 750 mg FCM Infusion Studies

Preferred Term	FCM (N=2566)	Pooled Comparators (N=2590)	Oral Iron (N=666)	Any IV Iron (N=1880)	Venofer (N=1678)	Other Comparators (N=44)
At Least 1 Serious Adverse Event	254 (9.9%)	246 (9.5%)	17 (2.6%)	227 (12.1%)	220 (13.1%)	2 (4.5%)
Cardiac failure congestive	30 (1.2%)	29 (1.1%)	0	29 (1.5%)	29 (1.7%)	0
Pneumonia	17 (0.7%)	18 (0.7%)	1 (0.2%)	17 (0.9%)	17 (1.0%)	0
Anemia	18 (0.7%)	7 (0.3%)	0	6 (0.3%)	6 (0.4%)	1 (2.3%)
Renal failure acute	14 (0.5%)	14 (0.5%)	1 (0.2%)	13 (0.7%)	13 (0.8%)	0
Gastrointestinal hemorrhage	13 (0.5%)	11 (0.4%)	0	11 (0.6%)	11 (0.7%)	0

Reviewer's Table

The percentage of subjects who had a treatment-emergent serious adverse event considered related to study drug was 0.2% in the FCM group, 0.5% in the any IV iron group, and 0.4% in the pooled comparators groups. Treatment-emergent serious adverse events considered related to study drug in the FCM group were arrhythmia, supraventricular tachycardia, constipation, anaphylactoid reaction, hypersensitivity, and liver function test abnormal (1 subject each, <0.1%).

7.3.3 Dropouts and/or Discontinuations

Primary Maximum 750 mg FCM Infusion Studies

In the primary maximum 750 mg FCM infusion studies, the overall incidence of treatment-emergent adverse events resulting in premature discontinuation of study drug was 2.9% in the FCM group, 2.3% in the Venofer group, and 2.1% in the pooled comparators group.

The most common treatment-emergent adverse events resulting in premature discontinuation of study drug in the FCM group were flushing and hypertension (0.5% and 0.6%, respectively).

All Maximum 750 mg FCM Infusion(s) Studies

In the all maximum 750 mg FCM infusion studies, the overall incidence of treatment-emergent adverse events resulting in premature discontinuation of study drug was 2.5% in the FCM group, 3.2% in the any IV iron group, and 2.6% in the pooled comparators group.

7.3.4 Significant Adverse Events

Cardiovascular Safety Composite Endpoint

In two pivotal clinical trials (1VIT09031 and 1VIT09031) included in the primary maximum 750 mg FCM infusion studies, the primary safety endpoint was the cardiovascular safety composite endpoint. The cardiovascular safety composite endpoint consisted of the following endpoints and was adjudicated by the Clinical Events Classification (CEC) committee of the (b) (4) :

- Deaths due to any cause
- Nonfatal myocardial infarction
- Nonfatal Stroke
- Unstable angina requiring hospitalization
- Congestive heart failure requiring hospitalization or medical intervention
- Arrhythmias
- Hypertension
- Hypotension

The following are definitions of these adjudicated endpoints:

1). Death due to any cause

2). Myocardial infarction

A myocardial infarction will be defined as the presence of the characteristic changes in cardiac enzyme markers in the setting of either temporally related symptoms of an acute coronary syndrome or ECG changes consistent with either ischemia or infarction.

Cardiac enzyme markers indicative of an MI will include:

- An appropriate rise and fall in serum troponin (I or T) or CKMB where at least one value is ≥2 x ULN. Where only one value has been measured, if it is ≥2 x ULN, an event may be adjudicated based on the totality of the clinical evidence.
- Where only total CPK is measured, serial changes (i.e. at least two values) need to be ≥2 xULN.
- Symptoms indicative of ischemia will need to have been present for ≥10 minutes and may include chest pain, chest pressure, or chest tightness. Dyspnea, diaphoresis, or nausea may be considered symptoms of ischemia and will be judged based on the totality of the clinical evidence.
- ECG changes will be defined as:
  - New Q waves in two or more contiguous leads
  - Evolving ST-segment to T-wave changes in two or more contiguous leads (such as ≥0.5mm transient ST segment depression)
  - New LBBB

- 1 mm ST segment elevation in two or more contiguous leads

3). Stroke

A stroke is defined as a focal neurological deficit of sudden onset that is not reversible within 24 hours that results from a vascular cause involving the CNS and is not due to another readily identifiable cause (i.e., brain tumor or trauma). Strokes will be sub-classified as hemorrhagic, ischemic, or unknown.

4). Unstable angina requiring hospitalization

Unstable angina requiring hospitalization will be defined as ischemic symptoms meeting the following criteria:
- lasting ≥ 10 minutes and considered to be myocardial ischemia on final diagnosis AND
- requiring unscheduled visit to a healthcare facility and overnight admission (does not include chest pain observation units) AND
- at least one of the following:
  - New dynamic ECG changes
  - Ischemia evidence on stress testing with or without cardiac imaging
  - Angiographic evidence of ≥ 70% lesion and/or thrombus in an epicardial coronary artery

5). Congestive heart failure requiring hospitalization or medical intervention

Congestive heart failure events will meet the following criteria:
- Requires hospitalization defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 12 hour stay (or a date change if the time of admission/discharge is not available) AND
- Clinical manifestation of CHF including at least one of the following: New or worsening-dyspnea, orthopnea, paroxysmal nocturnal dyspnoea, edema, pulmonary basilar crackles, jugular venous distension, or radiological evidence of worsening heart failure AND
- Additional/increased therapy
  - Intravenous treatment with diuretic, inotrope, or vasodilator therapy OR
  - Mechanical or surgical intervention (mechanical circulatory support, heart transplantation or ventricular pacing to improve cardiac function,) or the use of ultrafiltration, hemofiltration or dialysis that is specifically directed at treatment of heart failure.

6). Arrhythmia

Arrhythmia will be defined as any symptomatic deviation from normal sinus rhythm experienced by the subject that results in an evaluation by a health care provider. The evaluation may include a physical exam during an outpatient visit, an ECG, or a hospital admission. Arrhythmias may include any conduction abnormality, atrioventricular heart block, prolongation

of QTc interval, supraventricular/nodal arrhythmia, vasovagal episode, ventricular arrhythmia, or other cardiovascular arrhythmia.

7). Hypertension

- During the observation period immediately following study drug administration, hypertension will be defined as an increase in systolic blood pressure >20 mm Hg that results in a value >180 mm Hg or a increase in diastolic blood pressure >15 mm Hg that results in a value >105 mm Hg
- Following the release of a subject from the study visit during which they are receiving medication, hypertension will be defined as requiring an unscheduled outpatient healthcare visit, a hospital admission, or a change in medical therapy (e.g., administration of antihypertensives) in conjunction with the objective criteria a rise in blood pressure (an increase in systolic blood pressure >20 mm Hg that results in a value >180 mm Hg or a increase in diastolic blood pressure >15 mm Hg that results in a value >105 mm Hg).

8). Hypotension

- During the observation period immediately following study drug administration, hypotension will be defined as a decrease in systolic blood pressure >20 mm Hg that results in a value <90 mm Hg or a decrease in diastolic blood pressure >15 mm Hg that results in a value <50 mm Hg
- Following the release of a subject from the study visit during which they are receiving medication, hypotension will be defined as requiring an unscheduled outpatient healthcare visit, a hospital admission, or a change in medical therapy (e.g., fluid/volume repletion, . holding of antihypertensives) in conjunction with the objective criteria a decrement in blood pressure (a decrease in systolic blood pressure >20 mm Hg that results in a value <90 mm Hg or a decrease in diastolic blood pressure >15 mm Hg that results in a value <50mmHg).

In the primary maximum 750 mg FCM infusion studies, a total of 192 subjects (10.82%) in the FCM group, 172 subjects (9.65%) in the pooled comparators group, and 167 subjects (11.11%) in the Venofer group experienced at least one composite event for the primary composite safety endpoint. The difference with 95% CI was 1.17% (-0.88% to 3.22%) between FCM and pooled comparators and -0.29% (-2.50% to 1.91%) between FCM and Venofer. The inclusion of zero difference in the 95% CI suggested the difference was not statistically significant in cardiovascular risk between FCM and pooled comparators or Venofer based on pooled analysis.

A summary of the components of the primary composite safety endpoint in the pnmary maximum 750 mg FCM infusion studies is presented by treatment group in table below.

Table 35. The Results of the Primary Composite Safety Endpoint in Primary Maximum 750 mg FCM Infusion Studies

Composite Safety Endpoint	FCM (N=1775) n/N (%)	Pooled Comparators (N=1783) n/N (%)	Oral Iron (N=253) n/N (%)	Venofer (N=1503) n/N (%)
Any composite event	192 (10.82%)	172 (9.65%)	4 (1.58%)	167 (11.11%)
Components of composite endpoint0				
Death due to any cause	16 (0.90%)	21 (1.18%)	2 (0.79%)	19 (1.26%)
Nonfatal myocardial infarction	9 (0.51%)	14 (0.79%)	0	14 (0.93%)
Nonfatal stroke	3 (0.17%)	4 (0.22%)	1 (0.40%)	3 (0.20%)
Unstable angina requiring hospitalization	11 (0.62%)	4 (0.22%)	1 (0.40%)	3 (0.20%)
Congestive heart failure	38 (2.14%)	34 (1.91%)	0	34 (2.26%)
Arrhythmia	18 (1.01%)	14 (0.79%)	1 (0.40%)	13 (0.86%)
Protocol-defined hypertensive events	106 (5.97%)	62 (3.48%)	0	62 (4.13%)
Protocol-defined hypotensive events	27 (1.52%)	47 (2.64%)	1 (0.40%)	45 (2.99%)
Composite endpoint, excluding protocol-defined hypotensive and hypertensive events	72 (4.06%)	74 (4.15%)	4 (1.58%)	70 (4.66%)
Death, myocardial infarction, or stroke	26 (1.46%)	39 (2.19%)	3 (1.19%)	36 (2.40%)

a Includes oral iron, Venofer, and other forms of IV iron.
b Subjects may have experienced more than 1 component of the composite safety endpoint.
Reviewer's Table

The most common component of the primary composite safety endpoint was protocol-defined hypertensive events in the FCM, Venofer, and pooled comparators (5.97%, 4.13%, and 3.48%, respectively) groups.

The results of the primary composite safety endpoint was similar in subgroups by the etiology of IDA, ESA use and baseline hemoglobin category in the primary maximum 750 mg FCM infusion studies (see Table below).

Table 36. Primary Composite Safety Endpoint by Etiology of IDA, ESA Use, and Baseline hemoglobin in Primary Maximum 750 mg FCM Infusion Studies

	FCM (N=1775) n/N (%)	Pooled Comparators• (N=1783) n/N (%)	Oral Iron (N=253) n/N (%)	Venofer (N=1503) n/N (%)
All Subjects	192/1775 (10.82%)	172/1783 (9.65%)	4/253 (1.58%)	167/1503 (11.11%)
Etiology of IDA				
HUB	7/237 (2.95%)	3/233 (1.29%)	0/124	3/98 (3.06%)
Gastrointestinal	2/85 (2.35%)	6/83 (7.23%)	1/27 (3.70%)	4/44 (9.09%)
CKD	175/1276 (13.71%)	156/1285 (12.14%)	0/0	156/1285 (12.14%)
Other	8/177 (4.52%)	7/182 (3.85%)	3/102 (2.94%)	4/76 (5.26%)
ESAb				
No	146/1046 (13.96%)	132/1057 (12.49%)	0/0	132/1057 (12.49%)
Yes	29/230 (12.61%)	24/228 (10.53%)	0/0	24/228 (10.53%)

Baseline hemoglobin				
≤ 9.0 g/dL	21/248 (8.47%)	19/246 (7.72%)	0/24	18/212 (8.49%)
9.1 to 10.0 g/dL	55/394 (13.96%)	40/400 (10.00%)	3/48 (6.25%)	37/343 (10.79%)
>10.1 g/dL	116/1133 (10.24%)	113/1137 (9.94%)	1/181 (0.55%)	112/948 (11.81%)

Reviewer's Table

The pooled comparators group included non-CKD subjects who received oral iron in 1VIT09031 and were at lower cardiovascular risk than the CKD subjects who received FCM in 1VIT09030. The majority of the primary composite safety endpoint events were from the Study 1VIT09030 in CKD patients

The following tables show the results of the primary composite safety endpoint in each individual study.

In Study 1VIT09031, the overall event rate was low and all 7 subjects in the FCM group experienced hypertensive/hypotensive events. Hypertension and hypotension events were higher in the FCM group as compared to the oral iron group in Cohort 1 and were similar between the FCM and the other iron products in the Cohort 2.

Table 37. Primary Composite Safety Endpoint in Study 1VIT09031

	Cohort 1		Cohort 2	
	FCM (N=246)	Oral Iron (N=253)	FCM (N=253)	IVSC (N=245)
Any composite event	7 (2.85%)	4 (1.58%)	10 (3.95%)	12 (4.90%)
Components of Composite Endpoint'				
Death due to any cause	0	2 (0.79%)	1 (0.40%)	1 (0.41%)
Nonfatal myocardial infarction	0	0	1 (0.40%)	0
Nonfatal stroke	0	1 (0.40%)	0	0
Unstable angina requiring hospitalization	0	1 (0.40%)	0	0
Congestive heart failure	0	0	0	0
Arrhythmias	0	1 (0.40%)	0	0
Protocol-defined hypertensive events	4 (1.63%)	0	7 (2.77%)	6 (2.45%)
Protocol-defined hypotensive events	3 (1.22%)	1 (0.40%)	1 (0.40%)	5 (2.04%)
Composite Endpoint Excluding Protocol-Defined Hypertensive and Hypotensive Events	0	4 (1.58%)	2 (0.79%)	1 (0.41%)
Death, Myocardial Infarction, or Stroke	0	3 (1.19%)	2 (0.79%)	1 (0.41%)

Reviewer's Table

In Study 1VIT09030, the primary composite cardiovascular safety endpoint was a pre-specified primary safety endpoint to be tested in the study. The difference between FCM and Venofer in the proportion of subjects experiencing the primary composite endpoint was evaluated with a 95% 2-sided CI. The difference with 95% CI was 1.57% (-1.10% to 4.25%) between FCM and Venofer, which suggested the difference was not statistically significant in cardiovascular risk between FCM and Venofer. For each component, hypertensive events were significantly higher

in the FCM group as compared to the Venofer group (7.45% and 4.36%, respectively, 95% CI: 1.19%-4.99%).The all deaths, nonfatal MI and hypotensive events were numerically lower in the FCM group as compared to the Venofer group. Unstable angina requiring hospitalization, CHF requiring hospitalization, and arrhythmia were numerically higher in the FCM group as compared to the Venofer group. The composite endpoint events excluding hypertensive/hypotensive events was similar between the two treatment groups.

Table 38. Primary Composite Safety Endpoint in Study 1VIT09030

Composite Safety Endpoint	FCM (N=l276) n (%)	Venofer (N=1285) n (%)	Difference (95% CI)
Any composite event	175 (13.71%)	156 (12.14%)	1.57% (-1.10%, 4.25%)
Components of the composite endpoint*			
Death due to any cause	15 (1.18%)	18 (1.40%)	-0.23% (-1.18%, 0.73%)
Nonfatal MI	8 (0.63%)	14 (1.09%)	-0.46% (-1.25%, 0.33%)
Nonfatal stroke	3 (0.24%)	3 (0.23%)	0.00% (-0.45%, 0.45%)
Unstable angina requiring hosp.	11 (0.86%)	3 (0.23%)	0.63% (-0.02%, 1.28%)
CHF requiring hosp.	38 (2.98%)	34 (2.65%)	0.33% (-1.03%, 1.69%)
Arrhythmias	18 (1.41%)	13 (1.01%)	0.40% (-0.53%, 1.32%)
Hypertensive events	95 (7.45%)	56 (4.36%)	3.09% (1.19%, 4.99%)
Hypotensive events	23 (1.80%)	41 (3.19%)	-1.39% (2.67%, -0.10%)
Composite endpoint excluding hypertensive and hypotensive events	70 (5.49%)	69 (5.37%)	0.12% (-1.72%, 1.95%)
Death myocardial infarction, or stroke	24 (1.88%)	35 (2.72%)	-0.84% (-2.08%, 0.40%)

CI=confidence interval; * Subjects may have experienced more than 1 component of the composite safety endpoint.
Reviewer's Table

Hypersensitivity/Allergic Reactions

Hypersensitivity/allergic reactions included any serious or severe treatment-emergent adverse event occurring on the day of dosing or the day after dosing that included any term in the standardized MedDRA query (SMQ) for anaphylactic reaction. This SMQ included 4 groups of adverse event terms:

Group A: Narrow terms pertaining to hypersensitivity reactions
Group B: Broad terms pertaining to respiratory reactions potentially related to hypersensitivity
Group C: Broad terms pertaining to skin reactions potentially related to hypersensitivity
Group D: Broad terms pertaining to cardiovascular reactions potentially related to hypersensitivity

Primary Maximum 750 mg FCM Infusion Studies

In the primary maximum 750 mg FCM infusion studies, the overall incidence of treatment-emergent hypersensitivity/allergic reactions was 1.5% in the FCM group, 1.6% in the Venofer group, and 1.5% in the pooled comparators group.

A summary of the treatment-emergent potential hypersensitivity/allergic reactions in the primary maximum 750 mg FCM infusion studies is presented in the following table.

Table 39. Treatment-Emergent Potential Hypersensitivity/Allergic Reactions in Primary Maximum 750 mg FCM Infusion Studies

Preferred Term	FCM (N=l775)	Pooled Comparators (N=l783)	Oral Iron (N=253)	Venofer (N=l503)
At Least 1 Adverse Event	26 (1.5%)	26 (1.5%)	1 (0.4%)	24 (1.6%)
Group B +C	16 (0.9%)	13 (0.7%)	1 (0.4%)	11 (0.7%)
Grou B+D	21 (1.2%)	22 (1.2%)	1 (0.4%)	20 (1.3%)
Group B+C+D	24 (1.4%)	25 (1.4%)	1 (0.4%)	23 (1.5%)
Group A	2 (0.1%)	1 (0.1%)	0	1 (0.1%)
Anaphylactic reaction	1 (0.1%)	1 (0.1%)	0	1 (0.1%)
Anaphylactoid reaction	1 (0.1%)	0	0	0
Group B	13 (0.7%)	10 (0.6%)	1 (0.4%)	8 (0.5%)
Acute respiratory failure	0	4 (0.2%)	0	3 (0.2%)
Asthma	3 (0.2%)	0	0	0
Bronchospasm	1 (0.1%)	1 (0.1%)	0	1 (0.1%)
Cough	2 (0.1%)	0	0	0
Dyspnea	5 (0.3%)	4 (0.2%)	1 (0.4%)	2 (0.1%)
Respiratory distress	0	1 (0.1%)	1 (0.4%)	0
Respiratory failure	1 (0.1%)	2 (0.1%)	0	2 (0.1%)
Wheezing	2 (0.1%)	0	0	0
Group C	3 (0.2%)	3 (0.2%)	0	3 (0.2%)
Angioedema	0	1 (0.1%)	0	1 (0.1%)
Flushing	1 (0.1%)	0	0	0
Edema	1 (0.1%)	0	0	0
Pruritus	1 (0.1%)	0	0	0
Rash	0	2 (0.1%)	0	2 (0.1%)
Group D	8 (0.5%)	12 (0.7%)	0	12 (0.8%)
Cardiac arrest	0	4 (0.2%)	0	4 (0.3%)
Cardio-respiratory arrest	2(0.1%)	3 (0.2%)	0	3 (0.2%)
Hypotension	6 (0.3%)	5 (0.3%)	0	5 (0.3%)

Group A: Narrow terms pertaining to hypersensitivity reactions
Group B: Broad terms pertaining to respiratory reactions potentially related to hypersensitivity
Group C: Broad terms pertaining to skin reactions potentially related to hypersensitivity
Group D: Broad terms pertaining to cardiovascular reactions potentially related to hypersensitivity
Reviewer's Table

All Maximum 750 mg FCM Infusion(s) Studies

In the all maximum 750 mg FCM infusion(s) studies, the overall incidence of treatment-emergent hypersensitivity/allergic reactions was 1.1% in the FCM group, 1.5% in the any IV iron group, and 1.1% in the pooled comparators group.

A summary of treatment-emergent potential hypersensitivity/allergic reactions in the all

maximum 750 mg FCM infusion(s) studies is presented in the table below.

Table 40. Treatment Emergent Potential Hypersensitivity/Allergic Reactions in All Maximum 750 mg FCM Infusion Studies

Group Preferred Term	FCM (N=2566)	Pooled Comparators (N=2590)	Oral Iron (N=666)	Any IV Iron (N=l880)	Venofer (N=l678)	Other Comparators (N=44)
At Least 1 Adverse Event	28(1.1%)	29 (1.1%)	1 (0.2%)	28 (1.5%)	25 (1.5%)	0
Group B+ C	18 (0.7%)	14 (0.5%)	1 (0.2%)	13 (0.7%)	11 (0.7%)	0
Group B+ D	23 (0.9%)	24 (0.9%)	1 (0.2%)	23 (1.2%)	21 (1.3%)	0
Group B+ C+ D	26 (1.0%)	27 (1.0%)	1 (0.2%)	26 (1.4%)	24 (1.4%)	0
Group A	2 (0.1%)	2 (0.1%)	0	2 (0.1%)	1 (0.1%)	0
Anaphylactic reaction	1 (<0.1%)	2 (0.1%)	0	2 (0.1%)	1 (0.1%)	0
Anaphylactoid reaction	1 (<0.1%)	0	0	0	0	0
Group B	15 (0.6%)	11 (0.4%)	1 (0.2%)	10 (0.5%)	8 (0.5%)	0
Acute respiratory failure	0	4 (0.2%)	0	4 (0.2%)	3 (0.2%)	0
Asthma	3 (0.1%)	0	0	0	0	0
Bronchospasm	2 (0.1%)	1 (<0.1%)	0	1 (0.1%)	1 (0.1%)	0
Cough	2 (0.1%)	0	0	0	0	0
Dyspnea	6 (0.2%)	5 (0.2%)	1 (0.2%)	4 (0.2%)	2 (0.1%)	0
Respiratory distress	1 (<0.1%)	1 (<0.1%)	1 (0.2%)	0	0	0
Respiratory failure	1 (<0.1%)	2 (0.1%)	0	2 (0.1%)	2 (0.1%)	0
Wheezing	2 (0.1%)	0	0	0	0	0
Group C	3 (0.1%)	3 (0.1%)	0	3 (0.2%)	3 (0.2%)	0
Angioedema	0	1 (<0.1%)	0	1 (0.1%)	1 (0.1%)	0
Flushing	1 (<0.1%)	0	0	0	0	0
Edema	1 (<0.1%)	0	0	0	0	0
Pruritus	1 (<0.1%)	0	0	0	0	0
Rash	0	2 (0.1%)	0	2 (0.1%)	2 (0.1%)	0
Group D	8 (0.3%)	13 (0.5%)	0	13 (0.7%)	13 (0.8%)	0
Cardiac arrest	0	4 (0.2%)	0	4 (0.2%)	4 (0.2%)	0
Cardio-respiratory arrest	2 (0.1%)	3 (0.1%)	0	3 (0.2%)	3 (0.2%)	0
Hypotension	6 (0.2%)	6 (0.2%)	0	6 (0.3%)	6 (0.4%)	0

Group A: Narrow terms pertaining to hypersensitivity reactions
Group B: Broad terms pertaining to respiratory reactions potentially related to hypersensitivity
Group C: Broad terms pertaining to skin reactions potentially related to hypersensitivity
Group D: Broad terms pertaining to cardiovascular reactions potentially related to hypersensitivity
Reviewer's Table

Phase 2/3 Short-Term IDA and CHF Studies

In the Phase 2/3 short-term IDA and CHF studies, the overall incidence of potential hypersensitivity/allergic reactions was 0.9% in the FCM group, 1.5% in the any IV iron group, and 0.8% in the pooled comparators group.

A summary of treatment-emergent potential hypersensitivity/allergic reactions in the Phase 2/3 short-term IDA and CHF studies is presented in table below.

Table 41. Treatment-Emergent Potential Hypersensitivity/Allergic Reactions in Phase 2/3 Short-Term IDA and CHF Studies

Group Preferred Term	FCM (N=5799)	Pooled Comparators (N=5272)	Oral Iron (N=2497)	Any IV Iron (N=2439)	Venofer (N=2196)	Other Comparators (N=336)
At Least 1 Adverse Event	51 (0.9%)	42 (0.8%)	4 (0.2%)	37 (1.5%)	34 (1.5%)	1 (0.3%)
Group B+ C	37 (0.6%)	26 (0.5%)	4 (0.2%)	21 (0.9%)	19 (0.9%)	1 (0.3%)
Group B+ D	31 (0.5%)	31 (0.6%)	3(0.1%)	27 (1.1%)	25 (1.1%)	1 (0.3%)
Group B+ C+ D	48 (0.8%)	40 (0.8%)	4 (0.2%)	35 (1.4%)	33 (1.5%)	1 (0.3%)
Group A	3 (0.1%)	2(<0.1%)	0	2 (0.1%)	1(<0.1%)	0
Anaphylactic reaction	1 (<0.1%)	2(<0.1%)	0	2 (0.1%)	1 (<0.1%)	0
Anaphylactoid reaction	1(<0.1%)	0	0	0	0	0
Shock	1(<0.1%)	0	0	0	0	0
GroupE	20 (0.3%)	17 (0.3%)	3(0.1%)	13 (0.5%)	11 (0.5%)	1 (0.3%)
Acute respiratory failure	1 (<0.1%)	5(0.1%)	0	5 (0.2%)	4 (0.2%)	0
Asthma	3 (0.1%)	1 (<0.1%)	1(<0.1%)	0	0	0
Bronchospasm	2(<0.1%)	1(<0.1%)	0	1 (<0.1%)	1(<0.1%)	0
Cough	2(<0.1%)	2(<0.1%)	0	2 (0.1%)	2(0.1%)	0
Dyspnoea	8 (0.1%)	8 (0.2%)	2(0.1%)	5 (0.2%)	3(0.1%)	1 (0.3%)
Respiratory distress	1(<0.1%)	1 (<0.1%)	1(<0.1%)	0	0	0
Respiratory failure	1 (<0.1%)	2(<0.1%)	0	2(0.1%)	2(0.1%)	0
Swollen tongue	1(<0.1%)	0	0	0	0	0
Wheezing	3(0.1%)	0	0	0	0	0

Group A: Narrow terms pertaining to hypersensitivity reactions
Group B: Broad terms pertaining to respiratory reactions potentially related to hypersensitivity
Group C: Broad terms pertaining to skin reactions potentially related to hypersensitivity
Group D: Broad terms pertaining to cardiovascular reactions potentially related to hypersensitivity
Reviewer's Table

7.3.5 Submission Specific Primary Safety Concerns

Injectafer was initially submitted under NDA 22-054 and the pooled clinical data showed a higher mortality with the higher dose (1000 mg as a single administration) studied as compared to oral iron. The two pivotal clinical trials submitted in this current NDA that studied a low dose regimen of Injectafer in patients who were intolerant to oral iron with assessment of mortality and cardiovascular safety were planned to mitigate those safety concerns (See Section 2.5).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Primary Maximum 750 mg FCM Infusion Studies

Common Treatment-Emergent Adverse Events

In the primary maximum 750 mg FCM infusion studies, at least 1 treatment-emergent adverse event was experienced by 60.3% of subjects in the FCM group, 59.0% of subjects in the Venofer group, and 55.2% of subjects in the pooled comparator group.

The most common (≥2.0%) treatment-emergent adverse events in the FCM group were nausea (11.4%), hypertension (8.6%), dizziness (4.3%), flushing (3.4%), headache (3.3%), vomiting (3.3%), diarrhea (3.2%), urinary tract infection (3.2%), hypotension (2.8%), hypophosphatemia (2.7%), constipation (2.3%), fatigue (2.3%), back pain (2.3%), peripheral edema (2.3%), and congestive heart failure (2.1%).

Adverse events that occurred more frequently (by ≥1%) with Injectafer than with pooled comparator were nausea, hypertension, flushing, vomiting, hypophosphatemia, back pain, hyperkalemia, ALT increased, injection site discoloration, and hot flush.

Adverse events that occurred more frequently (by ≥1%) with Injectafer than with Venofer were nausea, hypertension, flushing, vomiting, hypophsphatemia, ALT increased, and injection site discoloration. Adverse events that occurred more frequently (by ≥1%) with Venofer than with Injectafer were diarrhea, peripheral edema, dysgesusia, injection site pain, and injection site extravasation.

The following table shows the treatment-emergent adverse events that occurred in ≥0.5% of subjects in any treatment group in the primary maximum 750 mg FCM infusion studies.

Table 42. Most Common Treatment-Emergent Adverse Events (≥0.5% in FCM group) in Primary Maximum 750 mg FCM Infusion Studies

Preferred Term	FCM (N=l775)	Pooled Comparators (N=1783)	Oral Iron (N=253)	Venofer (N=1503)
At Least 1 Adverse Event	1071 (60.3%)	984 (55.2%)	84 (33.2%)	887 (59.0%)
Nausea	202 (11.4%)	71 (4.0%)	5 (2.0%)	65 (4.3%)
Hypertension	152 (8.6%)	109 (6.1%)	4 (1.6%)	104 (6.9%)
Dizziness	76 (4.3%)	63 (3.5%)	2 (0.8%)	60 (4.0%)
Flushing	60 (3.4%)	3 (0.2%)	0	3 (0.2%)
Headache	59 (3.3%)	68 (3.8%)	8 (3.2%)	59 (3.9%)
Vomiting	58 (3.3%)	37 (2.1%)	2 (0.8%)	35 (2.3%)
Diarrhea	56 (3.2%)	70 (3.9%)	5 (2.0%)	63 (4.2%)
Urinary tract infection	56 (3.2%)	43 (2.4%)	2 (0.8%)	41 (2.7%)
Hypotension	49 (2.8%)	59 (3.3%)	1 (0.4%)	55 (3.7%)
Hypophosphatemia	48 (2.7%)	2 (0.1%)	0	2 (0.1%)
Constipation	41 (2.3%)	37 (2.1%)	11 (4.3%)	26 (1.7%)
Fatigue	41 (2.3%)	43 (2.4%)	2 (0.8%)	41 (2.7%)
Back pain	41 (2.3%)	24 (1.3%)	0	23 (1.5%)
Edema peripheral	40 (2.3%)	54 (3.0%)	0	54 (3.6%)
Cardiac failure congestive	37 (2.1%)	37 (2.1%)	0	37 (2.5%)
Nasopharyngitis	34 (1.9%)	35 (2.0%)	8 (3.2%)	26 (1.7%)
Upper respiratory tract infection	33 (1.9%)	33 (1.9%)	1 (0.4%)	32(2.1%)
Hyperkalemia	31 (1.7%)	12 (0.7%)	0	12 (0.8%)
Dyspnea	29 (1.6%)	26 (1.5%)	1 (0.4%)	24 (1.6%)
Cough	29 (1.6%)	32 (1.8%)	3 (1.2%)	28 (1.9%)
ALT increased	27 (1.5%)	7 (0.4%)	1 (0.4%)	6 (0.4%)
Injection site discoloration	26 (1.5%)	6 (0.3%)	0	6 (0.4%)
Arthralgia	26 (1.5%)	31 (1.7%)	2 (0.8%)	29 (1.9%)
Dysgeusia	25 (1.4%)	42 (2.4%)	0	42 (2.8%)

Bronchitis	24 (1.4%)	27 (1.5%)	2 (0.8%)	25 (1.7%)
Hypoglycemia	24 (1.4%)	13 (0.7%)	1 (0.4%)	12 (0.8%)
Pneumonia	23 (1.3%)	22 (1.2%)	0	22 (1.5%)
Hot flush	23 (1.3%)	6 (0.3%)	0	6 (0.4%)
Contusion	23 (1.3%)	12 (0.7%)	0	12 (0.8%)
AST increased	23 (1.3%)	7 (0.4%)	1 (0.4%)	6 (0.4%)
Muscle spasms	23 (1.3%)	12 (0.7%)	1 (0.4%)	10 (0.7%)
Pain in extremity	23 (1.3%)	29 (1.6%)	2 (0.8%)	27 (1.8%)
Cellulitis	22 (1.2%)	16 (0.9%)	0	16(1.1%)
Sinusitis	21 (1.2%)	26 (1.5%)	3 (1.2%)	23 (1.5%)
Rash	21 (1.2%)	17 (1.0%)	1 (0.4%)	14 (0.9%)
Pruritus	20 (1.1%)	20 (1.1%)	1 (0.4%)	18 (1.2%)
Abdominal pain	19 (1.1%)	21 (1.2%)	7 (2.8%)	13 (0.9%)
Paraesthesia	19(1.1%)	6 (0.3%)	0	6 (0.4%)
GGT increased	18 (1.0%)	10 (0.6%)	2 (0.8%)	8 (0.5%)
Renal failure chronic	18 (1.0%)	17 (1.0%)	0	17(1.1%)
Anemia	17 (1.0%)	5 (0.3%)	0	5 (0.3%)
Injection site pain	17 (1.0%)	31 (1.7%)	0	31 (2.1%)
Pyrexia	17 (1.0%)	11 (0.6%)	0	11 (0.7%)
Renal failure acute	16 (0.9%)	18 (1.0%)	2 (0.8%)	16(1.1%)
Asthenia	14 (0.8%)	15 (0.8%)	3 (1.2%)	12 (0.8%)
Pharyngolaryngeal pain	12 (0.7%)	12 (0.7%)	4 (1.6%)	7 (0.5%)
Injection site extravasation	8 (0.5%)	24(1.3%)	0	24 (1.6%)

a Includes oral iron, Venofer, and other forms of IV iron.
Reviewer's Table

Drug-Related Treatment-Emergent Adverse Events

A greater incidence of any drug-related treatment-emergent adverse event was observed in the FCM group (23.5%) compared with the Venofer (17.3%) and pooled comparators (15.9%) groups. The most common (≥1.0%) drug-related treatment-emergent adverse events in the FCM group were nausea (7.2%), hypertension (3.8%), flushing (2.7%), hypophosphatemia (2.1%), dizziness (2.0%), vomiting (1.7%), injection site discoloration (1.4%), headache (1.2%), ALT increased (1.1%), and dysgesusia (1.1%).

The following table shows drug-related treatment-emergent adverse events that occurred in ≥0.5% of subjects in any treatment group in the primary maximum 750 mg FCM infusion studies. Adverse events that occurred more frequently (by ≥1%) with Injectafer than with pooled comparator and Venofer included nausea, hypertension, flushing, hypophosphatemia, vomiting, and injection site discoloration. Drug-related adverse events that occurred more frequently (by ≥1%) with Venofer than with Injectafer were hypotension and dysgeusia.

Table 43. Most Common Drug-Related Treatment-Emergent Adverse Events (≥ 0.5% in the FCM Group) in Primary Maximum 750 mg FCM Infusion Studies

Preferred Term	FCM (N=l775)	Pooled Comparators (N=1783)	Oral Iron (N=253)	Venofer (N=1503)
At Least 1 Related Adverse Event	418 (23.5%)	283 (15.9%)	16 (6.3%)	260 (17.3%)
Nausea	127 (7.2%)	32 (1.8%)	3 (1.2%)	28 (1.9%)
Hypertension	67 (3.8%)	33 (1.9%)	1 (0.4%)	31 (2.1%)
Flushing	48 (2.7%)	1 (0.1%)	0	1 (0.1%)
Hypophosphataemia	37 (2.1%)	2 (0.1%)	0	2 (0.1%)
Dizziness	36 (2.0%)	21 (1.2%)	0	20 (1.3%)
Vomiting	30 (1.7%)	9 (0.5%)	1 (0.4%)	8 (0.5%)
Injection site discoloration	25 (1.4%)	5 (0.3%)	0	5 (0.3%)
Headache	21 (1.2%)	16 (0.9%)	0	15 (1.0%)
ALT increased	20 (1.1%)	3 (0.2%)	0	3 (0.2%)
Dysgeusia	20 (1.1%)	37 (2.1%)	0	37 (2.5%)
Hypotension	18 (1.0%)	34 (1.9%)	0	32(2.1%)
Diarrhoea	16 (0.9%)	14 (0.8%)	0	13 (0.9%)
AST increased	16 (0.9%)	4 (0.2%)	0	4 (0.3%)
Hot flush	16 (0.9%)	2(0.1%)	0	2(0.1%)
Injection site pain	15 (0.8%)	25 (1.4%)	0	25 (1.7%)
Injection site irritation	13 (0.7%)	9 (0.5%)	0	9 (0.6%)
GGT increased	12 (0.7%)	5 (0.3%)	0	5 (0.3%)
Abdominal pain upper	10 (0.6%)	1 (0.1%)	0	1 (0.1%)
Hypersensitivity	11 (0.6%)	7 (0.4%)	0	6 (0.4%)
Paraesthesia	11 (0.6%)	3 (0.2%)	0	3 (0.2%)
Sneezing	11 (0.6%)	0	0	0
Rash	11 (0.6%)	3 (0.2%)	0	2 (0.1%)
Constipation	9 (0.5%)	16 (0.9%)	8 (3.2%)	8 (0.5%)
Feeling hot	8 (0.5%)	2 (0.1%)	0	2 (0.1%)

a Includes oral iron, Venofer, and other forms of IV iron.
Reviewer's Table

All Maximum 750 mg FCM Infusion(s) Studies

Common Treatment-Emergent Adverse Events

In the all maximum 750 mg FCM studies, at least 1 treatment-emergent adverse event was experienced by 56.4% of subjects in the FCM group, 57.7% of subjects in the any IV iron group, and 52.9% of subjects in the pooled comparators group.

Similar to the primary maximum 750 mg FCM infusion studies, the most common (≥2.0%) treatment-emergent adverse events in the FCM group were nausea, hypertension, dizziness headache, diarrhea, hypophsphatemia, vomiting, flushing, urinary tract infection, constipation, fatigue, hypotension, and back pain.

The following table shows the treatment-emergent adverse events that occurred in ≥1% of subjects in the FCM group the all maximum 750 mg FCM studies. Adverse events that occurred more frequently (by ≥1%) with Injectafer than with pooled comparator were nausea, hypertension, hypophosphatemia, and flushing. Adverse events that occurred more frequently (by 1%) with Injectafer than with Venofer were nausea, hypophsphatemia, flushing, and ALT increased. Adverse events that occurred more frequently (by ≥1%) with Venofer than with Injectafer were diarrhea, hypotension, peripheral edema, and dysgesusia.

Table 44. Most Common Treatment-Emergent Adverse Events (≥ 1.0% in the FCM Group) in All Maximum 750 mg FCM Infusion Studies

Preferred Term	FCM (N=2566)	Pooled Comparators (N=2590)	Oral Iron (N=666)	Any IV Iron (N=1880)	Venofer (N=1678)	Other Comparators (N=44)
At Least 1 AE	1448 (56.4%)	1369 (52.9%)	263 (39.5%)	1085 (57.7%)	976 (58.2%)	21 (47.7%)
Nausea	243 (9.5%)	124(4.8%)	27(4.1%)	94 (5.0%)	82 (4.9%)	3 (6.8%)
Hypertension	155 (6.0%)	113(4.4%)	6 (0.9%)	107 (5.7%)	105 (6.3%)	0
Dizziness	98 (3.8%)	89 (3.4%)	11 (1.7%)	76 (4.0%)	67 (4.0%)	2 (4.5%)
Headache	92 (3.6%)	101 (3.9%)	21 (3.2%)	79 (4.2%)	64 (3.8%)	1 (2.3%)
Diarrhea	81 (3.2%)	95 (3.7%)	20 (3.0%)	75 (4.0%)	70 (4.2%)	0
Hypophosphatemia	76 (3.0%)	3(0.1%)	0	2(0.1%)	2(0.1%)	1 (2.3%)
Vomiting	73 (2.8%)	68 (2.6%)	19 (2.9%)	48 (2.6%)	42 (2.5%)	1 (2.3%)
Flushing	67 (2.6%)	7 (0.3%)	0	7 (0.4%)	4 (0.2%)	0
Urinary tract infection	66 (2.6%)	57 (2.2%)	9 (1.4%)	48 (2.6%)	46 (2.7%)	0
Fatigue	64 (2.5%)	58 (2.2%)	8 (1.2%)	48 (2.6%)	42 (2.5%)	2 (4.5%)
Constipation	63 (2.5%)	76 (2.9%)	45 (6.8%)	28 (1.5%)	28 (1.7%)	3 (6.8%)
Hypotension	58 (2.3%)	62 (2.4%)	1 (0.2%)	61 (3.2%)	56 (3.3%)	0
Back pain	52 (2.0%)	33 (1.3%)	3 (0.5%)	29 (1.5%)	24 (1.4%)	1 (2.3%)
Upper respiratory	50 (1.9%)	44 (1.7%)	10 (1.5%)	34(1.8%)	34 (2.0%)	0
Edema peripheral	49 (1.9%)	70 (2.7%)	1 (0.2%)	68 (3.6%)	62 (3.7%)	1 (2.3%)
Nasopharyngitis	44 (1.7%)	48 (1.9%)	17 (2.6%)	31 (1.6%)	27 (1.6%)	0
Arthralgia	40 (1.6%)	45 (1.7%)	5 (0.8%)	38 (2.0%)	33 (2.0%)	2 (4.5%)
Pain in extremity	38 (1.5%)	37 (1.4%)	5 (0.8%)	32 (1.7%)	29 (1.7%)	0
Cardiac failure	37 (1.4%)	37 (1.4%)	0	37 (2.0%)	37 (2.2%)	0
ALT increased	37 (1.4%)	16 (0.6%)	8 (1.2%)	8 (0.4%)	6 (0.4%)	0
Dysgeusia	33 (1.3%)	54(2.1%)	1 (0.2%)	52 (2.8%)	51 (3.0%)	1 (2.3%)
Hyperkalem ia	33 (1.3%)	15 (0.6%)	1 (0.2%)	14 (0.7%)	13 (0.8%)	0
Cough	33 (1.3%)	43 (1.7%)	7(1.1%)	36 (1.9%)	32 (1.9%)	0
Muscle spasms	32 (1.2%)	14 (0.5%)	2 (0.3%)	12 (0.6%)	10 (0.6%)	0
Rash	32 (1.2%)	26 (1.0%)	2 (0.3%)	24 (1.3%)	15 (0.9%)	0
Dyspnea	32 (1.2%)	33 (1.3%)	1 (0.2%)	30 (1.6%)	24 (1.4%)	2 (4.5%)
AST increased	31 (1.2%)	15 (0.6%)	8 (1.2%)	7 (0.4%)	6 (0.4%)	0

Abdominal pain	30 (1.2%)	38 (1.5%)	14(2.1%)	23 (1.2%)	15 (0.9%)	1 (2.3%)
Contusion	29 (1.1%)	18 (0.7%)	2 (0.3%)	15 (0.8%)	14 (0.8%)	1 (2.3%)
Injection site discoloration	29 (1.1%)	7 (0.3%)	0	6 (0.3%)	6 (0.4%)	1 (2.3%)
Pruritus	29 (1.1%)	30 (1.2%)	1 (0.2%)	27 (1.4%)	19(1.1%)	2 (4.5%)
Bronchitis	27(1.1%)	34 (1.3%)	6 (0.9%)	28 (1.5%)	25 (1.5%)	0
Pyrexia	27 (1.1%)	17(0.7%)	1 (0.2%)	16 (0.9%)	14 (0.8%)	0
GGT increased	27(1.1%)	11 (0.4%)	2 (0.3%)	9 (0.5%)	8 (0.5%)	0
Hot flush	27(1.1%)	8 (0.3%)	1 (0.2%)	7 (0.4%)	6 (0.4%)	0
Sinusitis	26 (1.0%)	36 (1.4%)	7(1.1%)	28 (1.5%)	26 (1.5%)	1(2.3%)
Cellulitis	25 (1.0%)	19 (0.7%)	0	19 (1.0%)	19(1.1%)	0
Hypoglycemia	25 (1.0%)	13 (0.5%)	1 (0.2%)	12 (0.6%)	12 (0.7%)	0

Reviewer's Table

Drug-Related Treatment-Emergent Adverse Events

Similar to the primary maximum 750 mg FCM infusion studies, a greater incidence of any drug-related adverse event was observed in the FCM group (23.1%) compared with the pooled comparators (17.7%) group. The most common (≥1.0%) drug-related treatment-emergent adverse events in the FCM group were also nausea, hypertension, hypophosphatemia, flushing, dizziness, vomiting, headache, ALT increased, dysgesusia, and injection site discoloration (see Table below). Adverse events that occurred more frequently (by ≥1%) with Injectafer than with pooled comparator and Venofer included nausea, hypertension, hypophosphatemia, and flushing. Drug-related adverse events that occurred more frequently (by ≥1%) with Venofer than with Injectafer were hypotension and dysgesusia.

Table 45. Most Common Drug-Related Treatment-Emergent Adverse Events (≥ 0.5% in the FCM Group) in All Maximum 750 mg FCM Infusion Studies

Preferred Term	FCM (N=2566)	Pooled Comparators (N=2590)	Oral Iron (N=666)	Any IV Iron (N=1880)	Venofer (N=1678)	Other Comparators (N=44)
At Least 1 Related Adverse Event	594 (23.1%)	459 (17.7%)	93 (14.0%)	356 (18.9%)	299 (17.8%)	10 (22.7%)

Nausea	148 (5.8%)	67 (2.6%)	16 (2.4%)	49 (2.6%)	38 (2.3%)	2 (4.5%)
Hypertension	68 (2.7%)	33 (1.3%)	1 (0.2%)	32 (1.7%)	31 (1.8%)	0
Hypophosphatemia	62 (2.4%)	2 (0.1%)	0	2 (0.1%)	2 (0.1%)	0
Flushing	53 (2.1%)	4 (0.2%)	0	4 (0.2%)	2 (0.1%)	0
Dizziness	46 (1.8%)	28 (1.1%)	0	27 (1.4%)	24 (1.4%)	1 (2.3%)
Vomiting	33 (1.3%)	28 (1.1%)	9 (1.4%)	19 (1.0%)	14 (0.8%)	0
Headache	32 (1.2%)	35 (1.4%)	7 (1.1%)	28 (1.5%)	16 (1.0%)	0
ALT increased	30 (1.2%)	11 (0.4%)	7 (1.1%)	4 (0.2%)	3 (0.2%)	0
Dysgeusia	28 (1.1%)	47 (1.8%)	1 (0.2%)	46 (2.4%)	45 (2.7%)	0
Injection site discoloration	28 (1.1%)	6 (0.2%)	0	5 (0.3%)	5 (0.3%)	1 (2.3%)
AST increased	24 (0.9%)	12 (0.5%)	7 (1.1%)	5 (0.3%)	4 (0.2%)	0
Constipation	23 (0.9%)	52 (2.0%)	40 (6.0%)	10 (0.5%)	10 (0.6%)	2 (4.5%)
Diarrhoea	21 (0.8%)	23 (0.9%)	7(1.1%)	16 (0.9%)	14 (0.8%)	0
Hypotension	21 (0.8%)	37 (1.4%)	0	37 (2.0%)	33 (2.0%)	0
GGT increased	20 (0.8%)	5 (0.2%)	0	5 (0.3%)	5 (0.3%)	0
Injection site pain	20 (0.8%)	26 (1.0%)	0	25 (1.3%)	25 (1.5%)	1 (2.3%)
Hot flush	18 (0.7%)	2 (0.1%)	0	2(0.1%)	2 (0.1%)	0
Injection site irritation	17 (0.7%)	10 (0.4%)	0	10 (0.5%)	10 (0.6%)	0
Rash	16 (0.6%)	10 (0.4%)	0	10 (0.5%)	3 (0.2%)	0
Hypersensitivity	14 (0.5%)	16 (0.6%)	0	15 (0.8%)	7 (0.4%)	1 (2.3%)
Fatigue	13 (0.5%)	9 (0.3%)	3 (0.5%)	5 (0.3%)	5 (0.3%)	1 (2.3%)
Pruritus	13 (0.5%)	20 (0.8%)	0	18(1.0%)	10 (0.6%)	2 (4.5%)
Abdominal pain upper	12 (0.5%)	9 (0.3%)	6 (0.9%)	2(0.1%)	1 (0.1%)	1 (2.3%)
Paraesthesia	12 (0.5%)	4 (0.2%)	0	4 (0.2%)	4 (0.2%)	0
Sneezing	12 (0.5%)	0	0	0	0	0

Reviewer's Table

Phase 2/3 Short-Term IDA and CHF Studies

In the Phase 2/3 short-term IDA and CHF studies, at least 1 treatment-emergent adverse event was experienced by 48.1% of subjects in the FCM group, 54.4% of subjects in the any IV iron group, and 46.3% of subjects in the pooled comparators group.

Common Treatment-Emergent Adverse Events

The most common (≥2.0%) treatment-emergent adverse event in the FCM group were nausea, headache, hypertension, dizziness, and diarrhea. Adverse events that occurred more frequently (by 1%) with Injectafer than with pooled comparator and Venofer were hypophosphatemia and flushing. Adverse events that occurred more frequently (by ≥1%) with Venofer than with Injectafer were hypertension, diarrhea, hypotension, peripheral edema, and dysgesusia (See Table below).

Table 46. Most Common Treatment-Emergent Adverse Events (≥ 1.0% in the FCM Group) in Phase 2/3 Short-Term IDA and CHF Studies

Preferred Term	FCM (N=5799)	Pooled Comparators (N=5272)	Oral Iron (N=2497)	Any IV Iron (N=2439)	Venofer (N=2196)	Other Comparators (N=336)
At Least 1 Adverse Event	2787 (48.1%)	2442 (46.3%)	961 (38.5%)	1326 (54.4%)	1200 (54.6%)	155 (46.1%)

Nausea	304 (5.2%)	239 (4.5%)	121 (4.8%)	109 (4.5%)	97 (4.4%)	9 (2.7%)
Headache	246 (4.2%)	207 (3.9%)	98 (3.9%)	95 (3.9%)	79 (3.6%)	14 (4.2%)
Hypertension	204 (3.5%)	154 (2.9%)	20 (0.8%)	126 (5.2%)	123 (5.6%)	8 (2.4%)
Dizziness	147 (2.5%)	124 (2.4%)	35 (1.4%)	84 (3.4%)	75 (3.4%)	5 (1.5%)
Diarrhea	125 (2.2%)	161 (3.1%)	72 (2.9%)	85 (3.5%)	79 (3.6%)	4 (1.2%)
Nasopharyngitis	102 (1.8%)	90 (1.7%)	46 (1.8%)	39 (1.6%)	35 (1.6%)	5 (1.5%)
Urinary tract infection	101 (1.7%)	82 (1.6%)	30 (1.2%)	51(2.1%)	48 (2.2%)	1 (0.3%)
Vomiting	98 (1.7%)	111 (2.1%)	52(2.1%)	55 (2.3%)	49 (2.2%)	4 (1.2%)
Constipation	97 (1.7%)	264 (5.0%)	224 (9.0%)	29 (1.2%)	29 (1.3%)	11 (3.3%)
Fatigue	96 (1.7%)	79 (1.5%)	18(0.7%)	58 (2.4%)	52 (2.4%)	3 (0.9%)
Hypotension	94 (1.6%)	78 (1.5%)	1(<0.1%)	77 (3.2%)	69 (3.1%)	0
Edema peripheral	84 (1.4%)	88 (1.7%)	10 (0.4%)	73 (3.0%)	67 (3.1%)	5 (1.5%)
Hypophosphtemia	82 (1.4%)	3(0.1%)	0	2 (0.1%)	2 (0.1%)	1 (0.3%)
ALT increased	79 (1.4%)	43 (0.8%)	29 (1.2%)	14 (0.6%)	12 (0.5%)	0
Arthralgia	79 (1.4%)	64 (1.2%)	14 (0.6%)	47 (1.9%)	42 (1.9%)	3 (0.9%)
Back pain	79 (1.4%)	54 (1.0%)	16 (0.6%)	35 (1.4%)	28 (1.3%)	3 (0.9%)
Upper respiratory tract infection	78 (1.3%)	72 (1.4%)	33 (1.3%)	36 (1.5%)	36 (1.6%)	3 (0.9%)
Flushing	75 (1.3%)	8 (0.2%)	1(<0.1%)	7 (0.3%)	4 (0.2%)	0
Abdominal pain	72 (1.2%)	68 (1.3%)	34 (1.4%)	31 (1.3%)	23 (1.0%)	3 (0.9%)
Rash	69 (1.2%)	45 (0.9%)	16 (0.6%)	28(1.1%)	19 (0.9%)	1 (0.3%)
Pyrexia	64 (1.1%)	32 (0.6%)	12 (0.5%)	20 (0.8%)	17 (0.8%)	0
ST increased	62 (1.1%)	35 (0.7%)	26 (1.0%)	9 (0.4%)	8 (0.4%)	0
Dysgeusia	57 (1.0%)	60 (1.1%)	4 (0.2%)	55 (2.3%)	54 (2.5%)	1 (0.3%)

Reviewer's Table

Drug-Related Treatment-Emergent Adverse Events

The most common (≥1.0%) drug-related treatment-emergent adverse event m the FCM group was nausea, headache, hypertension, hypophosphatemia, dizziness, flushing, and ALT increased (see Table below). Adverse events that occurred more frequently (by ≥1%) with Injectafer than with Venofer were nausea and hypophosphatemia. Adverse events that occurred more frequently (by ≥1%) with Venofer than with Injectafer were hypotension and dysgesusia (see Table below).

Table 47. Most Common Drug-Related Treatment-Emergent Adverse Events (≥ 0.5% in the FCM Group) in Phase 2/3 Short-Term IDA and CHF Studies

Preferred Term	FCM (N=5799)	Pooled Comparators	Oral Iron (N=2497)	Any IV Iron (N=2439)	Venofer (N=2196)	Other Comparators
At Least 1 Related AE	1031 (17.8%)	864 (16.4%)	422 (16.9%)	407 (16.7%)	348 (15.8%)	35 (10.4%)

Nausea	179 (3.1%)	145 (2.8%)	87 (2.5%)	53 (2.2%)	42 (1.9%)	5 (1.5%)
Headache	79 (1.4%)	59(1.1%)	28(1.1%)	31 (1.3%)	19 (0.9%)	0
Hypertension	74 (1.3%)	36 (0.7%)	1(<0.1%)	35 (1.4%)	34 (1.5%)	0
Hypophosphatemia	68 (1.2%)	2(<0.1%)	0	2(0.1%)	2 (0.1%)	0
Dizziness	68 (1.2%)	41 (0.8%)	7 (0.3%)	31 (1.3%)	28 (1.3%)	3 (0.90/o)
Flushing	60 (1.0%)	4(0.1%)	0	4 (0.2%)	2 (0.1%)	0
ALT increased	58 (1.0%)	26 (0.5%)	20 (0.8%)	6 (0.2%)	5 (0.2%)	0
Dysgeusia	51 (0.9%)	53 (1.0%)	4 (0.2%)	49 (2.0%)	48 (2.2%)	0
AST increased	46 (0.8%)	24 (0.5%)	18 (0.7%)	6 (0.2%)	5 (0.2%)	0
Constipation	44 (0.8%)	218(4.1%)	200 (8.0%)	10 (0.4%)	10 (0.5%)	8 (2.4%)
Blood phosphorus decreased	41 (0.7%)	0	0	0	0	0
Rash	39 (0.7%)	14 (0.3%)	3(0.1%)	10 (0.4%)	3(0.1%)	1 (0.3%)
Vomiting	38 (0.7%)	46 (0.9%)	26 (1.0%)	19 (0.8%)	14 (0.6%)	1 (0.3%)
GGT increased	35 (0.6%)	6(0.1%)	1(<0.1%)	5 (0.2%)	5 (0.2%)	0
Injection site discoloration	32 (0.6%)	6 (0.1%)	0	5 (0.2%)	5 (0.2%)	1 (0.3%)
Diarrhea	30 (0.5%)	59(1.1%)	41 (1.6%)	18 (0.7%)	16 (0.7%)	0
Injection site pain	30 (0.5%)	28 (0.5%)	0	27(1.1%)	27 (1.2%)	1 (0.3%)
Injection site extravasation	30 (0.5%)	13 (0.2%)	0	13 (0.5%)	13 (0.6%)	0
Pruritus	27 (0.5%)	22 (0.4%)	1(<0.1%)	18 (0.7%)	10 (0.5%)	3 (0.9%)
Hypotension	27 (0.5%)	42 (0.8%)	0	42 (1.7%)	38 (1.7%)	0

Reviewer's Table

7.4.2 Laboratory Findings

A summary of the percentages of subjects with treatment-emergent potentially clinically significant (PCS) hematology values in the primary maximum 750 mg FCM infusion studies is presented in the following table. No clinically important differences were observed between the FCM group and the Venofer or pooled comparators groups in the percentage of subjects with treatment-emergent PCS hematology values.

Table 48. Treatment-Emergent Potentially Clinically Significant Hematology Values in Primary Maximum 750 mg FCM Infusion Studies

Parameter	FCM n/N (%)	Pooled Comparators n/N (%)	Oral Iron n/N (%)	Venofer n/N (%)
Lymphocytes -low	13/1624 (0.8%)	7/1639 (0.4%)	0/248	7/1368 (0.5%)
Neutrophils - low	3/1555 (0.2%)	3/1578 (0.2%)	1/220 (0.5%)	2/1334 (0.1%)
Platelets -low	2/1503 (0.1%)	1/1515 (0.1%)	1/204 (0.5%)	0/1292
WBC -low	1/1565 (0.1%)	0/1585	0/225	0/1337

Reviewer's Table

A summary of the percentages of subjects with treatment-emergent PCS chemistry values in the primary maximum 750 mg FCM infusion studies is presented in following table. The percentage of subjects with treatment-emergent PCS low phosphorus, defined as a baseline value that was less than Grade 3 and decreased to a value defined as Grade 3 (<2.0 - 1.0 mg/dL) or Grade 4 (<1.0 mg/dL) was greatest in the FCM group than in the Venofer and pooled comparators groups.

Table 49. Incidence of Subjects with Treatment-Emergent Potentially Clinically Significant Chemistry Values in Primary Maximum 750 mg FCM Infusion Studies

Parameter	FCM n/N(%)	Pooled Comparators n/N (%)	Oral Iron n/N (%)	Venofer n/N (%)
ALT/SGPT (U/L)	6/1688 (0.4%)	4/1672 (0.2%)	1/233 (0.4%)	3/1413 (0.2%)
AST/SGOT (U/L)	5/1665 (0.3%)	3/1676 (0.2%)	1/242 (0.4%)	2/1408 (0.1%)
Alkaline phosphatase (U/L)	0/1521	1/1537(0.1%)	0/232	1/1282(0.1%)
Calcium (mg/dL) - high	3/1684 (0.2%)	0/1685	0/249	0/1410
Calcium (mg/dL)-low	1/1684 (0.1%)	0/1685	0/249	0/1410
Creatinine (mg/dL)	1/1668 (0.1%)	0/664	0/230	0/409
GGT (UIL)	2/1534 (0.1%)	2/1555 (0.1%)	0/234	1/1296 (0.1%)
Magnesium (mg/dL)- high	11/1564 (0.7%)	9/1567 (0.6%)	0/247	9/1296 (0.7%)
Phosphorus (mg/dL) -low	440/1638 (26.9%)	12/1610 (0.7%)	1/249 (0.4%)	10/1335 (0.7%)
Serum bicarbonate (mEq/L)- low	4/1603 (0.2%)	7/1583 (0.4%)	0/235	7/1322 (0.5%)
Serum glucose (mg/dL)- high	19/961 (2.0%)	28/956 (2.9%)	3/193 (1.6%)	25/742 (3.4%)
Serum potassium (mEq/L) -high	13/1627 (0.8%)	13/1647 (0.8%)	1/248 (0.4%)	12/1374 (0.9%)
Serum potassium (mEq/L) -low	6/1627 (0.4%)	4/1647 (0.2%)	0/248	4/1374 (0.3%)
Serum sodium (mEq/L)- high	2/1595 (0.1%)	1/1612 (0.1%)	0/249	1/1340 (0.1%)
Serum sodium (mEq/L) -low	9/1595 (0.6%)	8/1612 (0.5%)	1/249 (0.4%)	7/1340 (0.5%)
Total bilirubin (mg/dL)	0/1403	1/1393 (0.1%)	0/199	1/1174 (0.1%)

Reviewer's Table

In Study 1VIT09030, all PCS low phosphorus events were CTCAE Grade 3, except for 1 event in an FCM subject that was CTCAE Grade 4. None of the low phosphorus events were associated with serious adverse events; however, 6 subjects (5 FCM and 1 Venofer) experienced adverse events of hypophosphatemia that were considered severe (Grade 3).

In Study 1VIT09031, all PCS low phosphorus events were CTCAE Grade 3, except for 6 events in subjects assigned to FCM that were CTCAE Grade 4. None of these were associated with serious or severe adverse events. One subject had events of somnolence, fatigue, tingling finger, swollen hand, and elevated WBC count on days when the phosphorus level was CTCAE Grade 4; all other events were Grade 1-2 and were considered by the Investigator to be unlikely related to FCM.

Baseline mean phosphorus values were similar across the FCM, Venofer, and pooled comparators groups (range: 4.01-4.06 g/dL) in primary maximum 750 mg FCM infusion studies. Greater mean decreases from baseline to the lowest and final values were observed in the FCM group (-1.37 and -0.56 g/dL, respectively) compared with the Venofer (-0.62 and -0.08 g/dL, respectively) and pooled comparators (-0.58 and -0.07 g/dL, respectively).

The median number of days to first value below reference range was 14 days in the FCM, Venofer, and pooled comparators groups. Additionally, among subjects whose phosphorus value returned to within reference range, median days to recovery was 21 days in the FCM group and 14 days in the Venofer and pooled comparators groups. Estimation of

these time courses is limited by the protocol-specified schedule of assessments in the 2 primary maximum 750 mg FCM infusion studies.

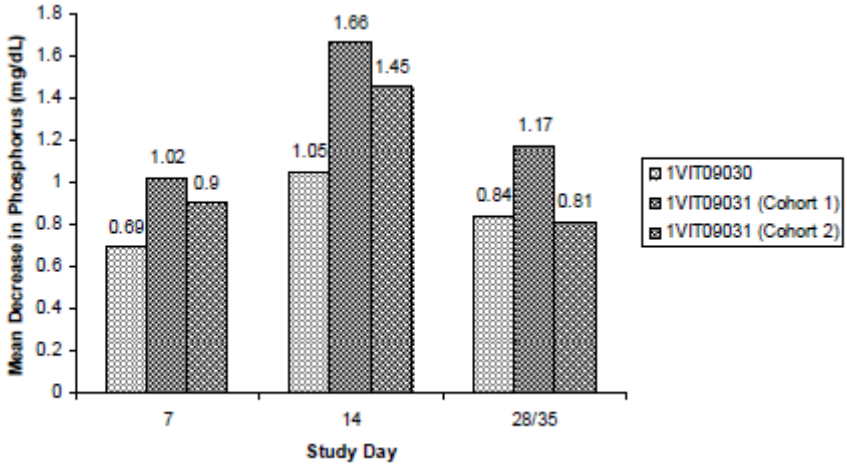
Table 50. Time Course for Serum Phosphorus in Primary Maximum 750 mg FCM Infusion Studies

Serum Phosphorus	FCM n/N(%)	Pooled Comparators n/N (%)	Oral Iron n/N (%)	Venofer n/N (%)
Baseline				
n	1754	1758	253	1479
Mean (SD)	4. 01 (0. 767)	4.03 (0.790)	3.84 (0.636)	4.06 (0.814)
Median	3.9	3.9	3.8	4.0
Minimum, Maximum	1.9, 10.2	2.0, 8.7	2.3, 8.7	2.0, 8.7
Change to Lowest Value				
n	1754	1758	253	1479
Mean (SD)	-1.37 (0.791)	-0.58 (0. 619)	-0.40 (0.589)	-0.62 (0.615)
Median	-1.4	-0. 6	-0.4	-0. 6
Minimum, Maximum	-7.0, 1.8	-5.1, 2.2	-5.1, 0.8	-3.8, 2.2
Change to Final Value				
n	1754	1758	253	1479
Mean (SD)	-0.56 (0.916)	-0.07 (0.694)	-0.07 (0.608)	-0.08 (0.704)
Median	-0.5	-0.1	-0.1	-0.1
Minimum, Maximum	-5.9, 4.5	-4.4, 2.7	-4.4, 1.7	-2.7, 2.7
Days to First Value Below Reference Range				
n	601	28	2	25
Mean(SD)	13.9 (7.57)	20.2 (13.98)	7.0 (0.00)	21.3 (14.28)
Median	14	14	7	14
Minimum, Maximum	6, 57	7,60	7, 7	7,60
Days to Return to Within Reference Range				
n	388	22	1	21
Mean(SD)	26.5 (13. 64)	19.9 (11.07)	7.0	20.5 (10.95)
Median	21	14	7	14
Minimum, Maximum	4, 94	7,42	7, 7	7,42

a Includes oral iron, Venofer, and other forms of IV iron.
b Only subjects with both a baseline and at least 1 post-baseline value were included in the analysis.
c Includes only subjects with a baseline ≥ lower reference range and at least 1 value below the lower reference range after baseline.
Reviewer's Table

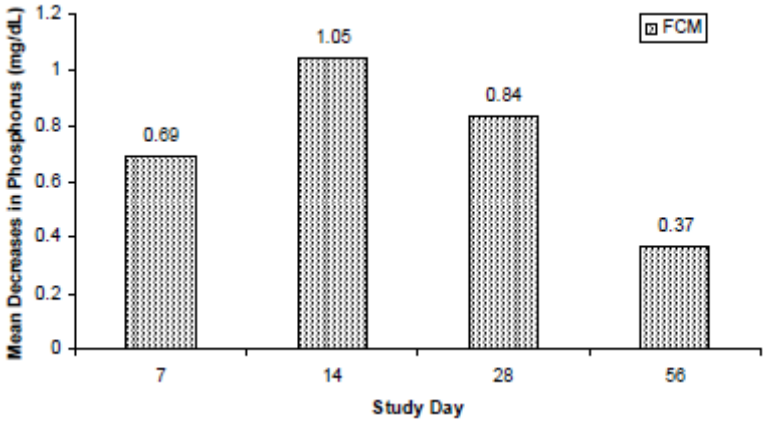
Mean decreases from baseline in phosphorus in the FCM group were highest at Day 14 and were returning toward baseline at Day 28/35 in Studies 1VIT09030 and 1VIT09031 (see Figure 2). The trend toward baseline continued through Day 56 in Study 1VIT09030 (see Figure 3).

Figure 8. Mean Decreases in Phosphorus in the FCM Group in Studies 1VIT09030 and 1VIT09031



Sponsor's figure

Figure 9. Mean Decreases in Phosphorus in the FCM Group in Study 1VIT09030



Sponsor's figure

7.4.3 Vital Signs

A summary of the incidence of subjects with treatment-emergent PCS vital signs after infusion is presented in Table below. The percentage of subjects with treatment-emergent PCS systolic BP was higher in the FCM group as compared to the Venofer groups (5.3% vs. 2.4%).

Table 51. Treatment-Emergent Potentially Clinically Significant Vital Signs after Infusion in Primary Maximum 750mg FCM Infusion Studies

Vital Sign (unit)	Potentially clinically significant (PCS) Criteria	FCM n/N(%)	Venofer n/N(%)	Any IV Iron n/N(%)
Systolic BP (mmHg)	≤90 mmHg and ↓≥20 mmHg from pre-dose value	12/1774 (0.7%)	15/1501 (1.0%)	16/1528 (1.0%)
	≥180 mmHg and ↑≥20 mmHg from pre-dose value	94/1774 (5.3%)	36/1501 (2.4%)	36/1528 (2.4%)
Diastolic BP (mmHg)	≤50 mmHg and ↓≥15 mmHg from pre-dose value	16/1774 (0.9%)	28/1501 (1.9%)	28/1528 (1.8%)
	≥105 mmHg and ↑≥15 mmHg from pre-dose value	23/1774 (1.3%)	16/1501 (1.1%)	16/1528 (1.0%)
Pulse	≤50 bpm and ↓≥15 bpm from pre-dose value	4/1774 (0.2%)	13/1501 (0.9%)	13/1528 (0.9%)
	≥120 bpm and ↑≥15 bpm from pre-dose value	0/1774	1/1501 (0.1%)	1/1528 (0.1%)

Reviewer's Table

7.4.4 Electrocardiograms (ECGs)

ECG was not performed for all patients in the clinical trials. For patients who developed cardiac symptoms ECG was used to assess cardiac safety endpoints (unstable angina and MI).

7.4.5 Special Safety Studies/Clinical Trials

Not performed.

7.4.6 Immunogenicity

Not performed.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Only one proposed dosing regimen of 15 mg/kg with the maximum single dose of 750 mg and the maximum cumulative dose of 1500 mg was studied in the two pivotal clinical trials. A high maximum single dose of 1000 mg with a high maximum cumulative dose of 2500 mg was studied in clinical trials for previous (NDA 22-054) submission that showed a mortality disadvantage of Injectafer as compared to oral iron.

7.5.2 Time Dependency for Adverse Events

Hypersensitivity reactions, hypertension/hypotension events occurred shortly after FCM injection.

7.5.3 Drug-Demographic Interactions

No study was specifically conducted to evaluate drug-demographic interactions.

The following are based on subgroup analyses from clinical trials.

Age
Among the primary maximum 750 mg FCM infusion studies, among FCM-treated patients, 896 subjects were <65 years of age, 879 (50%) subjects were ≥65 years of age, and 439 (25%) subjects were ≥75 years of age. The overall percentage of FCM subjects who experienced at least 1 treatment-emergent adverse event was 55.9% in subjects <65 years of age, 64.8% in subjects ≥65 years of age, and 63.8% in subjects ≥75 years of age.

For the most common treatment-emergent adverse events in the primary maximum 750 mg infusion studies, notably higher incidence rates of cardiac failure congestive and urinary tract infection were observed in subjects ≥65 years of age than subjects <65 years of age in the FCM group. The pattern for cardiac failure congestive was similar in the Venofer and pooled comparators groups.

Gender
For the most common treatment-emergent adverse events in the primary maximum 750 mg infusion studies, notably higher incidence rates of cardiac failure congestive and constipation were observed in males than females in the FCM group. Notably higher incidence rates of nausea, vomiting, back pain, headache, and flushing were observed in females than males in the FCM group. The patterns for cardiac failure congestive and headache were similar in the Venofer and pooled comparators groups.

Race
For the most common treatment-emergent adverse events in the primary maximum 750 mg infusion studies, notably higher incidence rates of diarrhea, urinary tract infection, and hypotension were observed in Caucasian than non-Caucasian subjects in the FCM group. The patterns for diarrhea and hypotension were similar in the Venofer and pooled comparators groups.

7.5.4 Drug-Disease Interactions

No studies were specifically conducted to evaluate the Drug-Disease Interactions interaction. There were no PK studies conducted evaluating the effect of FCM in special population (renal or hepatic impaired) subjects.

The following are based on subgroup analyses from clinical trials.

Etiology of IDA
For the most common treatment-emergent adverse events for FCM subjects in the primary maximum 750 mg infusion studies, the following lists some differences in common AEs among subgroups with different etiology of IDA. It appears that patients with CKD experienced more AEs than other subgroups, as expected, except for hypophosphatemia:

- hypophosphatemia (8.0% in the HUB subgroup compared with 3.5%, 2.8%, and 1.6% in the gastrointestinal, other, and CKD subgroups, respectively)
- headache (5.5%, 4.7% and 3.2% in the HUB, gastrointestinal, and CKD subgroups compared with 0.6% in the other subgroup)
- nausea (13.5% in the CKD subgroup compared with 6.2% and 5.1% in the other and HUB subgroups, respectively)
- dizziness (4.8%, 3.0%, and 4.0% in the CKD, HUB, and other subgroups, respectively, compared with 1.2% in the gastrointestinal subgroup)
- hypertension (10.7% in the CKD subgroup compared with 4.5%, 2.5%, and 2.4% in the other, HUB, and gastrointestinal subgroups, respectively)
- urinary tract infection (3.8% in the CKD subgroup compared with 0% and 1.1% in the gastrointestinal and other subgroups, respectively, and 2.1% in the HUB subgroup compared with 0% in the gastrointestinal subgroup)
- diarrhea (3.8% in the CKD subgroup compared with 1.7% and 0% in the HUB and other subgroups, respectively, and 3.5% in the gastrointestinal subgroup compared with 0% in the other subgroup)
- flushing (3.8% in the CKD subgroup compared with 2.4% in the gastrointestinal subgroup)
- back pain (5.1% and 4.7% in the other and gastrointestinal subgroups, respectively, compared with 2.0% and 0.8% in the CKD and HUB subgroups, respectively)
- vomiting (3.8% and 2.8% in the CKD and other subgroups, respectively, compared with 0.8% in the HUB subgroup)
- hypotension (3.1% in the CKD subgroup compared with 1.1% in the other subgroup)

7.5.5 Drug-Drug Interactions

No drug-drug interaction studies were conducted.

The following are based on subgroup analyses from clinical trials.

ESA Use
For the most common treatment-emergent adverse events in the primary maximum 750 mg infusion studies, notably higher incidence rates of diarrhea and headache were observed in non-ESA users than ESA users in the FCM group. The pattern for headache was similar in the Venofer and pooled comparators groups.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No carcinogenicity study was conducted.

7.6.2 Human Reproduction and Pregnancy Data

Nineteen subjects (11 in FCM-treated patients and 8 in control-treated patients) became pregnant during study in FCM development program. Of the 11 FCM subjects who became pregnant, 4 were lost to follow-up, 4 terminated their pregnancy, 2 had normal deliveries with no complications, and 1 was ongoing as of last follow-up. Of the 8 comparator subjects who became pregnant, 4 were lost to follow-up, 3 had a spontaneous abortion, and 1 was terminated.

7.6.3 Pediatrics and Assessment of Effects on Growth

No pediatric studies were conducted. The applicant requested a deferral of pediatric studies in (b)(4) and 17 years of age group under PMRs and requested a waiver of a pediatric study in the 0-(b)(4) years of age group to meet the requirements of Pediatric Research Equity Act (PREA). The proposed pediatric studies in (b)(4) and 17 years of age group include one pharmacokinetic/ pharmacodynamic study and one safety and efficacy study in pediatric patients with iron deficiency anemia. The applicant proposed to submit full pediatric study protocols within one year of approval and recruitment will begin within the first 18 months after the NDA is approved with the final study report being submitted on or before December 31, 2016.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No formal studies have been conducted to evaluate the abuse potential, withdrawal and rebound effect.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

FCM has been marketed outside of the US since 2007 under 3 different trade names: Ferinject®, Injectafer®, and Iroprem®, varying by country. As of 17 June 2011, the product is approved for use and marketed in 20 European countries. It has been approved but it has not yet been marketed in 15 other countries. The estimated exposure was 285,572 patient-years based on the number of sold ampoules as of 17 June 2011. Ferinject is indicated for treatment of iron deficiency when oral iron preparations are ineffective or cannot be used in the Summary of Product Characteristics in U.K.

A total of 8 deaths have been spontaneously reported since has been marketed. Seven fatal cases were reported prior to 31 December 2010 and are listed in the table below. Of the 7 cases, 2 cases have been considered to be possibly related to FCM as per reporter. The other cases have been assessed to be not related to FCM per reporter. Vifor's assessment is included in the Table below.

Table 52. Deaths from Post-marketing Spontaneous Reports

Vifor MCN	Age/ Gender/ Country	Report Type	Underlying Diseases	Event Term/ Cause of Death	Reporter Causality	Medical Comment
2008-00398	Elderly/F/ German	HCP	Chronic IDA, HF, CAD, COPD, PVD	Unknown cause of death/death cause unknown	Not related	Autopsy was not conducted. Confounded by multiple comorbidities of severe cardiac and pulmonary diseases which may be alternative explanation for the patient's death.
2009-00202	85/M/ Switzerland	HCP	CKD, HF, CAD, alcohol abuse, COPD	Acute liver failure acute bronchopneumonia	Not assessed	Autopsy confirmed cause of death to be acute bronchopneumonia and expanded recent hepatic necrosis. Patient had signs of liver stasis prior to Ferinject® treatment. Confounded by multiple concomitant medications associated with increased liver enzymes.
2009-00621	65/M/ Germany	NIS	Laryngeal carcinoma with pulmonary metastasis	Cerebral insult	Possibly related	Event started during second dose of Ferinject (200 mg/50 mL/3 min) (b) (6) days after the first. MI or pulmonary embolism was not confirmed. Autopsy was not performed. A contributory role of Ferinject cannot be excluded.
2009-01273	Elderly/F/ Germany	NIS	CKD, HF, CAD, COPD, PVD	Pneumonia	Not related	The underlying diseases provide alternative explanation. Died more than (b) (6) months from end of Ferinject treatment.
2010-00752	69/F/UK	HA	CKD, DM, PVD	Death unexplained	Possibly related by HA but not related by reporting physician	Patient died at home the next morning after Ferinject infusion. The time interval between finishing Ferinject infusion at the hospital and going home was not reported. It is difficult to determine if Ferinject played a role.
2010-01493	96/M/ Germany	NIS	Prostate carcinoma	Prostate carcinoma worsening	Not related	The underlying disease provides alternative explanation. Died (b) (6) months from end of Ferinject treatment.
2010-01494	80/M/ Germany	NIS	CKD, IDA, AOD, prostate cancer, malignant melanoma, stomach tumour	Stroke	Not related	The underlying diseases provide alternative explanation. Died about (b) (6) months from end of Ferinject treatment.

Notes: AOD = Arterial occlusive disease; CAD = Coronary artery disease; CKD = Chronic kidney disease; COPD = Chronic obstructive pulmonary disease; DM = Diabetes mellitus; F = Female; HA = Health Authority; HF = Heart failure; IDA = Iron deficiency anaemia; M = Male; MCN = Manufacturer control number; MI = Myocardial infarction; NIS = Non-interventional study; PVD = Peripheral vascular disease.

Sponsor's Table

One additional case was reported between December 2010 and June 2011. This fatal case concerns a male patient (NOS), with a medical history of metastatic gastric cancer (lymph

nodes) who was receiving palliative care for a year. The patient received 500 mg iron as Ferinject as an IV infusion for anemia and experienced elevated liver enzymes and thrombocytopenia 3-4 weeks later. The patient died due to disease progression. The reporter and Vifor considered the events unrelated to Ferinject administration.

European Union Summary of Product Characteristics (SPC) has been updated to include the addition of "anaphylactoid reaction, which may be potentially fatal" in the Special Warnings and Precautions for Use Section and amending the Undesirable Effects section to include "hypersensitivity including anaphylactoid reactions" and "dyspnea". A variation was submitted during the period of Periodic Safety Update Report (PSUR) for Ferinject in February 2011 adding hypertension to the SPC; it is still under review. Areas of special interest including hyperkalemia, urinary tract infection, bronchitis, hypertension, bilirubin increased, infusion site reactions, cardiac disorders, hypersensitivity, hypophosphatemia, hemosiderosis, and fatal events continue to be monitored and presented in the PSURs.

A summary of spontaneous, literature and related solicited cases of FCM (including investigator-initiated trials) included in Ferinject PSURs from 18 June 2007 to 17 June 2011 is presented in the following table.

Table 53. PSUR Cumulative Summary Tabulations of Adverse Events by MedDRA SOC

SOC	Adverse Events[a]	Serious Adverse Events	Non-serious Adverse Events	Total
Infections and infestations	1	2	1	4
Blood and lymphatic disorders	5	4	8	17
Immune system disorders	19	135	33	187
Endocrine disorders		1	-	1
Metabolism and nutrition disorders	-	6	2	8
Psychiatric disorders		7	10	19
Nervous system disorders	-	40	102	166
Eye disorders	2	6	13	19
Ear and labyrinth disorders	24	6	11	21
Cardiac disorders		13	16	33
Vascular disorders	4	20	33	58
Respiratory, thoracic and mediastinal disorders	4	47	23	78
Gastrointestinal disorders	5	36	87	158
Hepatobiliary disorders	8	1	-	3
Skin and subcutaneous disorders	35	100	291	498
Musculoskeletal, connective tissue and bone disorders	2	21	44	86
Renal and urinary disorders	107	3	1	4
Pregnancy, puerperium and perinatal conditions	21	1	1	2
Reproductive system and breast disorders	-	4	1	7
General disorders and administration site conditions	-	94	561	778
Investigations	2	13	31	52
Injury poisoning and procedural complications	123	21	46	81
Surgical and medical procedures	8	1	3	4
Social circumstances	14	-	1	1
Total	384	582	1,319	2,285

Note: Due to conventions used by Vifor Pharma in collecting related solicited cases, some of the events included in the table are from cases reported as related serious adverse events in clinical trials sponsored by Luitpold Pharmaceuticals, Inc.
a Compiled from PSURs PVZ-VIT45/E02 and PVZ-VIT45/E03, which combined the counts of serious and non-serious adverse events.
Reviewer's table

The following serious adverse reactions have been reported frequently in post-marketing spontaneous reports: urticaria, dyspnea, pruritus, hypersensitivity reactions, nausea, rash, hypotension, tachycardia, vertigo, vomiting, abdominal pain, diarrhea, chills, injection site discoloration, erythema, pyrexia, chest discomfort, dizziness, headache, malaise, angioedema, anaphylactic shock, feeling hot, flushing, collapse, hypertension, and syncope.

9 Appendices

9.1 Literature Review/References

N/A

9.2 Labeling Recommendations

This reviewer has the following recommendations for the following sections of the proposed labeling:

- Indication and Usage (Section 1):
  - The indication should be revised to

    "for the treatment of iron deficiency anemia in patients who were intolerant to oral iron or have had unsatisfactory response to oral iron and in patients with non-dialysis dependent chronic kidney disease".

- Dosage and Administration (Section 2):
  - Only slow undiluted injection was studied in two clinical trials for the proposed dosing regimen. Administration by diluted infusion has not been studied for the intended population for the proposed regimen. Consider to delete the administration by diluted infusion.

  - Add the following in this section:

    " Injectafer should be carefully administered to avoid extravasation. Due to the brown color of intravenous iron preparations, extravasation may lead to injection site discoloration which may be long lasting. In case of extravasation, the administration must be stopped immediately."
    "Inspect parenteral drug products visually for the absence of particulate matter and discoloration prior to administration.

- Warnings and Precautions (Section 5):
  - As for other intravenous iron products, hypersensitivity reactions should be highlighted in bold letters.
  - Add Hypertension subsection as follows:

"In clinical studies, hypertension was reported in 6% (106/1,775) of subjects. Transient elevations in systolic blood pressure, sometimes occurring with facial flushing, dizziness, or nausea were observed in clinical trials. These elevations generally occurred immediately after dosing and resolved within 30 minutes. Monitor patients closely for signs and symptoms of hypertension following each Injectafer administration [*see Dosage and Administration (2)* and *Warnings and Precautions (5.1)*]."

– (b) (4)

– Revise Iron Overload section as follows:

"Excessive therapy with parenteral iron can lead to excess storage of iron with the possibility of iatrogenic hemosiderosis. Regularly monitor the hematologic response during parenteral iron therapy [*see Dosage and Administration (2)*]. Do not administer Injectafer to patients with iron overload."

- Adverse Reactions (Section 6):
  - Revise to include safety information including common adverse reaction table from the two pivotal clinical trials that supported the proposed Injectafer dosing regimen as follows:

"In two randomized clinical studies [Studies 1 and 2, *See Clinical Studies (14)*], a total of 1,775 patients were exposed to Injectafer 15 mg/kg body weight up to a maximum single dose of 750 mg of iron on two occasions separated by at least 7 days up to a cumulative dose of 1500 mg of iron.

Adverse reactions reported by ≥ 1% of treated patients are shown the following table.

Table 1. Adverse reactions reported in ≥ 1% of Study Patients in Clinical Trials

Term	FCM (N=1775) %	Any other IV iron (N=1783) %	Oral iron (N=253) %
Nausea	7.2	1.8	1.2
Hypertension	3.8	1.9	0.4
Flushing/Hot Flush	3.6	0.2	0.0
Hypophosphatemia	2.1	0.1	0.0
Dizziness	2.0	1.2	0.0
Vomiting	1.7	0.5	0.4
Injection Site Discoloration	1.4	0.3	0.0
Headache	1.2	0.9	0.0
Alanine Aminotransferase Increased	1.1	0.2	0.0
Dysgeusia	1.1	2.1	0.0
Hypotension	1.0	1.9	0.0
Constipation	0.5	0.9	3.2
Diarrhea	0.5	0.9	0.0

Other adverse reactions reported by ≥ 0.5% of treated patients include abdominal pain, gamma glutamyl transferase increased, injection site pain/irritation, rash, paraesthesia, sneezing. Transient

decreases in laboratory blood phosphorus levels (< 2 mg/dL) have been observed in 27% (440/1638) patients in clinical trials."

- (b) (4)

- Use in Specific Populations (Section 8):
  - Revise the Geriatric Use subsection to comply with 21 CFR 201.57 as follows:

"Of the 1775 subjects in clinical studies of Injectafer, 50% were 65 years and over, while 25% were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out."

- Overdosage (section 10):
  - Revise as follows

"Excessive dosages of Injectafer may lead to accumulation of iron in storage sites potentially leading to hemosiderosis. Do not administer Injectafer to patients with iron overload [*Warnings and Precautions (5.3)*]."

- Clinical Studies (Section 14):
  - Revise the section as follows

"14 CLINICAL STUDIES
The safety and efficacy of Injectafer for treatment of iron deficiency anemia were evaluated in two randomized, open-label, controlled clinical trials (Trial 1 and Trial 2). In these two trials, Injectafer was administered at dose of 15 mg/kg body weight up to a maximum single dose of 750 mg of iron on two occasions separated by at least 7 days up to a cumulative dose of 1500 mg of iron.

14.1 Trial 1: Iron Deficiency Anemia in Patients Who Are Intolerant to Oral Iron or Have Had Unsatisfactory Response to Oral Iron

Trial 1 was a randomized, open-label, controlled clinical study in patients with iron deficiency anemia who had unsatisfactory response to oral iron (Cohort 1) or who were intolerant to oral iron (Cohort 2) during the 14 day oral iron run-in period. Inclusion criteria prior to randomization included hemoglobin (Hb) <12 g/dL, ferritin between 100 ng/mL and 300 ng/mL with transferrin saturation (TSAT) ≤ 30%. Cohort 1 subjects were randomized to Injectafer or oral iron for 14 more days. Cohort 2 subjects were randomized to Injectafer or another IV iron per standard of care [90% of subjects received iron sucrose]. The mean age of study patients was 43 years (range, 18 to 94); 94% were female; 42% were Caucasian, 32% were African American, 24% were Hispanic, and 2% were other races. The primary etiologies of iron deficiency anemia were heavy uterine bleeding (47%) and gastrointestinal disorders (17%).

Table 2 shows the baseline and the change in hemoglobin from baseline to highest value between baseline and Day 35 or time of intervention.

Table 2. Mean Change in Hemoglobin From Baseline to the Highest Value Between Day 35 or Time of Intervention (Modified Intent-to-Treat Population)

Hemoglobin (g/dL) Mean (SD)	Cohort 1		Cohort 2	
	Injectafer (N=244)	Oral Iron (N=251)	Injectafer (N=245)	IV SC[a] (N=237)
Baseline	10.6 (1.0)	10.6 (1.0)	9.1 (1.6)	9.0 (1.5)
Highest Value	12.2 (1.1)	11.4 (1.2)	12.0 (1.2)	11.2 (1.3)
Change to Highest Value	1.6 (1.2)	0.8 (0.8)	2.9 (1.6)	2.2 (1.3)
p-value	0.001		0.001	

SD=standard deviation; [a]: Intravenous iron per standard care

Increases from baseline in mean ferritin (264.2±224.2 ng/mL in Cohort 1 and 218.2 ±211.4 ng/mL in Cohort 2), and transferrin saturation (13±16% in Cohort 1 and 20±15%) were observed at Day 35 in Injectafer-treated patients.

14.2 Trial 2: Iron Deficiency Anemia in Patients with Non Dialysis Dependent Chronic Kidney Disease

Trial 2 was a randomized, open-label, controlled clinical study in patients with non dialysis dependent chronic kidney disease. Inclusion criteria included hemoglobin (Hb) ≤ 11.5 g/dL, ferritin between 100 ng/mL and 300 ng/mL with transferrin saturation (TSAT) ≤ 30%. Study patients were randomized to either Injectafer or Venofer. The mean age of study patients was 67 years (range, 19 to 96); 64% were female; 54% were Caucasian, 26% were African American, 18% were Hispanics, and 2% were other races.

Table 3 shows the baseline and the change in hemoglobin from baseline to highest value between baseline and Day 56 or time of intervention.

Table 3. Mean Change Hemoglobin From Baseline to the Highest Value Between Baseline and Day 56 or Time of Intervention (Modified Intent-to-Treat Population)

Hemoglobin (g/dL) Mean (SD)	Injectafer (N=1249)	Venofer (N=1244)
Baseline	10.3 (0.8)	10.3 (0.8)
Highest Value	11.4 (1.2)	11.3 (1.1)
Change to Highest Value	1.1 (1.0)	0.9 (0.92)
Treatment Difference (95% CI)	0.21 (0.13, 0.28)	

Increases from baseline in mean ferritin (734.7±337.8 ng/mL), and transferrin saturation (30±17%) were observed at Day 56 in Injectafer-treated patients."

- Delete studies that were not used to support the proposed dosing regimen

- Patient Counseling Information:
  - Revise as follows:

    - Question patients regarding any prior history of reactions to parenteral iron products.
    - Advise patients of the risks associated with Injectafer.
    - Advise patient to report any signs and symptoms of hypersensitivity that may develop during and following Injectafer administration, such as rash, itching, dizziness, lightheadedness, swelling and breathing problems [*see Warnings and Precautions (5)*]

9.3 Advisory Committee Meeting

There was no Advisory Committee Meeting for this review cycle.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MIN LU
06/08/2012

KATHY M ROBIE SUH
06/08/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 203565 **Applicant:** Luitpold Pharmaceuticals, Inc. **Stamp Date:** October 3, 2011

Drug Name: Injectafer **NDA/BLA Type:** 000

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.,* Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:		x		
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: Study 1VIT09031 A Multi-center, Randomized, Active Controlled Study to	x			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Investigate the Efficacy and Safety of Intravenous Ferric Carboxymaltose (FCM) in Patients With Iron Deficiency Anemia Pivotal Study #2: Study 1VIT09030 Randomized Evaluation of Efficacy and Safety of Ferric Carboxymaltose in Patients With Iron Deficiency Anemia and Impaired Renal Function Indication: Treatment of iron deficiency anemia.				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?		x		
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	x			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	x			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	x			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and	x			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	adverse dropouts (and serious adverse events if requested by the Division)?				
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			Also see Statistical review
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			Also see Statistical review
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			Also see Statistical review
34.	Are all datasets to support the critical safety analyses available and complete?	x			Also see Statistical review
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			Also see Statistical review
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _____Yes___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. The proposed indication of Injectafer as first line treatment of iron deficiency anemia may not be supported by the efficacy and safety results of Study 1VIT09031. By design, the study was conducted in patients who were intolerant to oral iron or who had inadequate response to oral iron during the run-in period. Adequacy of the study to support the proposed indication is a review issue.

2. All safety results should be included under Adverse Reactions section of labeling.

/electronic signature/

Reviewing Medical Officer Date

/electronic signature/

Clinical Team Leader Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MIN LU
12/15/2011

KATHY M ROBIE SUH
12/15/2011

M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: March 7, 2008

From: Kathy M. Robie-Suh, M.D., Ph.D.
Medical Team Leader, Hematology
Division of Medical Imaging and Hematology Drugs (HFD-160)
Office of Oncology Drug Products, CDER

Subject: Secondary Review
NDA 22-054, Complete Response to Not Approvable Letter, submitted 9/12/07 (received 9/13/07)
Ferinject (VIT-45, iron carboxymaltose) for treatment of iron deficiency anemia in heavy uterine bleeding and postpartum anemia
Sponsor: Luitpold Pharmaceuticals, Inc.

To: NDA 22-054

Ferinject (iron carboxymaltose) is an iron formulation developed for parenteral administration to treat iron deficiency anemia as an alternative to oral iron. The original NDA was submitted on June 15, 2006 for the treatment of iron deficiency anemia in: heavy uterine bleeding, postpartum, inflammatory bowel disease (IBD) and hemodialysis patients. The NDA is notable for its dosing recommendation to administer iron repletion as a single dose up to 1000 mg elemental iron infusion, as compared to usual administration of 100-200 mg (400 mg in peritoneal dialysis) of elemental iron as a maximum daily dose for other approved parenteral iron products. The application received a non-approval action on July 9, 2007 because of an unfavorable benefit/risk relationship for the patients with iron deficiency anemia targeted for use of the product, particularly with regard to a mortality disadvantage for Ferinject.

Though ability of Ferinject to raise hemoglobin levels in iron deficient patients was demonstrated in the controlled clinical studies for these indications, review of the safety data found a number of critical safety concerns. The safety data for the clinical studies showed a striking imbalance in mortality between the Ferinject and control treated patients, with most deaths occurring within 30 days of last Ferinject dose. Across the studies in the original submission there were 10 deaths among Ferinject treated patients and no deaths in the control (oral iron treated) patients. Submission of safety data an ongoing study added one death among control (Venofer-treated) patients in a pilot study of Injectafer in chronic heart failure patients (FER-CARS-01). Examination of the safety data also revealed a higher rate of serious adverse reactions, clinically important hypophosphatemia (<2 mg/dL) and a suggestion of increased cardiac toxicity with Injectafer. Deficiencies also were identified with regard to lack of data from repeat treatment cycles, limited experience in geriatric patients and lack of sufficient clinical data with lower doses of Ferinject to adequately assess concern that the safety risks were related to excessive Ferinject dosages. (See previous Clinical Reviews, Dr.

M. Lu, 5/31/07 and Dr. K. Robie-Suh, 6/29/07 and Statistical Review, S. C. Misra, Ph.D., 6/26/07). In the Not Approvable letter the sponsor (b) (4) The studies also should thoroughly assess the risk and clinical implications for hypophosphatemia in these patients and provide a risk management plan to address this concern. The letter also required that clinical data to support the safety of repeated iron replenishment cycles be provided.

In the complete response to the Not Approvable letter the sponsor provided (1) clinical study reports for a randomized controlled (oral iron) trial of Ferinject in the treatment of anemia in non-dialysis dependent chronic kidney disease (CKD) patients (Study 1VIT04004) and an open-label, long-term safety extension study in non-dialysis dependent CKD patients (Study 1VIT05005); (2) a revised updated integrated summary of safety (ISS) incorporating all available safety data; (3) a statistical position paper on the mortality rates for Ferinject; (4) a summary paper describing and providing evaluations of all the deaths and a narrative response to the deficiencies in the Not Approvable letter. Shortly after the complete response resubmission the sponsor amended the application to restrict the indication to post-partum women and women with heavy uterine bleeding. The proposed dose continues to be the calculated iron dose required for repletion administered intravenously as a single dose of 1000 mg of iron weekly until the total calculated dose has been administered or a total cumulative dose of 2500 mg. Accordingly, the resubmission has been reviewed with both the revised target population (post partum women and women with heavy uterine bleeding) and the recommended dosing regimen in mind.

Second cycle review has consisted of review by clinical (Dr. M. Lu, completed 2/28/08, signed 3/6/08), Pediatric and Maternal Health Team (Dr. K. Feibus, completed 12/7/07 and 1/11/08, signed 12/18/07 and 1/24/08), Division of Reproductive and Urologic Products (DRUP)(G. Willett, M.D., completed 12/7/07, signed 12/10/07); Statistics (Y-T. Wu, Ph.D., 12/6/07; S. C. Misra, 2/27/08), Office of Surveillance and Epidemiology (OSE)/Division of Epidemiology (S. Iyasu, M.D., M.P.H., 2/29/08), OSE/Division of Drug Risk Evaluation (C. Dormitzer, Ph.D., 1/22/08), Clinical Pharmacology (C. John, Ph.D., 2/21/08), and Chemistry, Manufacturing and Controls (CMC), (E. Leutzinger, 2/19/08). The application also was presented and discussed at a meeting of the Drug Safety and Risk Management (DSARM) Advisory Committee on 2/1/08.

Comments:
The sponsor has responded to the Division's Not Approvable letter for Injectafer (iron carboxymaltose), an injectable iron product, which was not approved because of serious safety concerns, including a mortality risk with the product. In the resubmission the sponsor has narrowed the target population to exclude very ill patients (b) (4) however, in doing so the remaining target population---post partum women and women with heavy uterine bleeding--- for this drug is a healthy population that most commonly is able to take iron orally. Indeed, in all the clinical trials to support use of Injectafer in these populations the control used has been oral iron and in these studies hemoglobin of women improved over baseline on both oral iron and Injectafer. Considering the usual good health and available alternative of oral iron for these

patients a high level of safety is required for a recommendation of approval for a parenteral iron product in these populations.

The safety database consisted of 9 randomized, parallel, controlled studies, 1 randomized, controlled cross-over study and 4 uncontrolled studies. [Note: These include two randomized controlled studies in women with heavy uterine bleeding that are considered as one study; these two studies were discontinued prematurely due to slow enrollment and the data from the two were pooled for analysis]. Overall mortality in all randomized, parallel group, controlled clinical studies was 0.41% (5/1206) for Injectafer and 0.10% (1/994) for control (oral iron, Venofer or placebo) patients. Deaths by patient population exposed in the controlled clinical studies are summarized in the following table:

Summary of Deaths in Controlled Studies

Study population	Injectafer Group	Control Group[a]
Post-partum anemia		
Number of patients exposed	543	442
Number of deaths	1	0
Heavy uterine bleeding		
Number of patients exposed	230	226
Number of deaths	0	0
Inflammatory bowel disease		
Number of patients exposed	137	63
Number of deaths	1	0
Hemodialysis		
Number of patients exposed	119	118[b]
Number of deaths	1	0
Iron deficiency anemia (mixed population)(cross-over study)		
Number of patients exposed	584	569[c]
Number of deaths	1	0
Non-hemodialysis CKD		
Number of patients exposed	147	103
Number of deaths	2	0
Chronic heart failure		
Number of patients exposed	30	27[b] + 15[c]
Number of deaths	0	1[b]

[a] control is oral iron unless otherwise specified; [b] Venofer; [c] placebo

based on Clinical Review (Dr. M. Lu, 2/28/08), Section 5.3

Among 341 patients treated in uncontrolled clinical studies of Ferinject, there were 4 deaths (2 in hemodialysis patients and 2 in non-hemodialysis chronic kidney disease patients). All these cases of death are presented in detail in the Clinical Review by Dr. Lu.

The additional information provided by the sponsor does not provide meaningful insight into the cause for the mortality imbalance observed with Ferinject. Lower planned doses have not been adequately studied to evaluate any possible influence of dose on this imbalance. The Clinical Pharmacology review (C. John, Ph.D., 2/21/08) commented that there was not much difference in transferrin saturation amongst the highest dose groups (500 mg, 800 mg and 1000 mg) and recommended that a lower dose of Injectafer be studied further. The collective safety

information suggests that Ferinject may predispose patients to adverse cardiovascular events which may lead to death. There was a statistically significant greater mortality in the Ferinject treated patients (0.49%) as compared to the comparator (oral iron or Venofer)-treated patients (0.0%) in the controlled clinical trials.

The two clinical trials in non-hemodialysis patients that were included in the resubmission contributed an additional approximately 200 patients exposed to Ferinject to the database. Most of these patients were treated according to the 1000 mg single dose regimen. [Note: The two deaths among Ferinject patients in these studies were previously reported in the original NDA while the studies were ongoing]. Findings of decreases in serum phosphate with Ferinject in these studies were consistent with those of the other studies and were greater in the Ferinject arm than in oral iron comparator. The clinical review found that in the oral iron controlled studies there was an imbalance in serious adverse events, particularly for serious cardiac events and serious infection events, against Ferinject (SAEs: 3.2% and 2.5%; Cardiac SAEs: 0.9% and 0.4%; infection SAEs: 0.9% and 0.4%, for Injectafer and oral iron, respectively)(Clinical Review, Dr. M. Lu, 2/28/08).

The Statistical review concluded based on analysis of the 9 controlled studies in the database "that the stratified analyses suggests that the mortality risk was numerically greater in the (Injectafer) ferric carboxymaltose-treated group (6 deaths) compared to the control-treated group (1 death) with point estimate of odds ratio >1 and risk difference >0, but the 0.05 significance level was not reached in some of these sensitivity analyses performed using different statistical approaches. The safety signal of increased mortality risk associated with ferric carboxymaltose could not be ruled out." (Statistical review, S. C. Misra, 2/27/08). The DSARM Advisory Committee found (12 yes/ 2 no/ 2 abstain) that Injectafer was associated with a mortality disadvantage compared to oral iron and recommended that the available efficacy and safety data did not support (14 not support/ 2 support/ 1 abstain) a favorable benefit-risk assessment for Injectafer for the treatment of iron deficiency anemia in post partum women or women with heavy uterine bleeding, not otherwise restricted. A smaller majority of the committee (10 yes/ 5 no/ 2 abstain) felt there may be a role for Injectafer in post-partum women or women with heavy uterine bleeding who have had an unsatisfactory response to oral iron or were intolerant of oral iron.

Review of the safety findings by groups within CDER having special expertise and focus on maternal and reproductive health and epidemiology also expressed serious concerns for safety in the target populations. The OSE/Division of Risk Evaluation review (C. Dormitzer, Ph.D., 1/22/08) found that the studies were too disparate to support a formal meta-analysis; however, they found the trend of increased mortality with Ferinject to be a serious concern and commented that "…the observation of FCM [Ferinject]-related deaths suggests a trend of increased cardiac mortality that could be more pronounced in post-marketing exposures given that a larger number of patients would be treated and that more vulnerable groups would be likely to receive the treatment." The Pediatric and Maternal Health Team (Dr. K. Feibus, 12/7/07) concluded that: "The three studies conducted by Luipold in postpartum women do not support first line parenteral iron therapy with Injectafer in the iron-deficient postpartum population as a whole. While hemoglobin levels increased more rapidly and ferritin levels were more completely restored, two of the three studies did not demonstrate a significant difference in hemoglobin gains at the end of the study period. In addition, studies that

included quality of life measures did not demonstrate an advantage of Injectafer over ferrous sulfate." The review expressed concern over the apparent cardiac death in a 38 year old post partum woman with no previous cardiac history and the hypophosphatemia seen among patients in the studies. The Division of Reproductive and Urologic Products review (Dr. G. Willett, 12/10/07) also expressed concern for the death in the heavy uterine bleeding study and questioned the diagnosis of peripartum cardiomyopathy in this patient. The review commented: "This consultant concurs with DMIHP's serious safety concerns for this product due to the large difference in mortality when comparing Injectafer to the control population. The unexplained hypophosphatemia is also a major safety concern. There is no pressing unmet medical need for a parenteral product to treat IDA in postpartum patients and patients with heavy uterine bleeding." The review concluded that, "The risk:benefit analysis in these healthy patient populations requires products to have very little risk, which does not appear to be the case given the safety findings for Injectafer." The Division of Epidemiology of OSE commented on the safety findings and DSARM Advisory Committee discussions and concluded: "Based on the safety data from the clinical development program, assessment of benefit risk considerations, and the availability of safer alternatives, OSE concludes that the mortality risks with Injectafer exceed whatever clinical benefits may accrue from its use in the treatment of iron deficiency anemia inwomen with postpartum anemia or women with heavy uterine bleeding. OSE recommends non-approval of Injectafer for the proposed indication of iron deficiency anemia in post partum women and women with heavy uterine bleeding." (S. Iyasu, M.D., M.P.H., 2/29/08).

Chemistry (CMC) review (E. Leutinzer, 2/19/08) found no deficiencies that would preclude approval.

Conclusions and Recommendations:
I concur with the recommendation of the primary clinical review (Dr. M. Lu, 2/28/08) that Injectafer should not be approved for the treatment of iron deficiency anemia for the proposed population of post-partum women and women with heavy uterine bleeding. The mortality findings in the clinical database indicate that use of Injectafer in these two essentially healthy populations is unacceptably risky, particularly considering that most of these patients may be adequately treated with oral iron.

Approval of Injectafer for use in the subset of oral iron intolerant (or refractory) patients in these populations may be possible but this must be supported by demonstration of "a clinically meaningful benefit in addition to hemoglobin increase" and "a favorable benefit over risk" in clinical trials as recommended in the Clincal Review. As recommended in the Clinical Review a large randomized safety trial needs to be conducted to evaluate the mortality risk and serious cardiac risk of Injectafer (e.,g, comparing Injectafer with oral iron and another IV iron product); this should be done in a population that may appropriately benefit from parenteral iron. In addition, further work needs to be done to examine the effect of Injectafer on serum phosphate levels and possible clinical consequences. These additional safety data are needed to provide adequate labeling for Injectafer in the event efficacy with no safety signal are seen in an adequate-and well-controlled clinical study for the intolerant/refractory population. The sponsor should also consider investigating use of lower single doses of Injectafer in these patients as a possible means of minimizing adverse safety outcomes in these patients.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kathy Robie-Suh
3/11/2008 11:19:59 AM
MEDICAL OFFICER

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: June 29, 2007

From: Kathy M. Robie-Suh, M.D., Ph.D.
Medical Team Leader, Hematology
Division of Medical Imaging and Hematology Drugs (HFD-160)
Office of Oncology Drug Products, CDER

Subject: Secondary Review
NDA 22-054, submitted 6/16/06
Ferinject (VIT-45, iron carboxymaltose) for treatment of iron deficiency anemia in heavy uterine bleeding, postpartum, inflammatory bowel disease and hemodialysis patients
Sponsor: Luitpold Pharmaceuticals, Inc.

To: NDA 22-054

Ferinject (iron carboxymaltose) is an iron preparation formulated for intravenous (IV) administration for use in treatment of iron deficiency anemia. Ferinject is an aqueous isotonic colloidal solution of polynuclear iron (III) hydroxide in complex with carboxymaltose. It has not been approved for marketing anywhere in the world.

The sponsor is seeking an indication stated as follows:

> "**1 INDICATIONS AND USAGE**
> Ferinject is indicated for the treatment of iron deficiency anemia in:
> **1.1 Heavy Uterine Bleeding**
> **1.2 Postpartum**
> **1.3 Inflammatory Bowel Disease (IBD)**
> **1.4 Hemodialysis patients**"

The sponsor has studied Ferinject in limited numbers of patients with iron deficiency anemia in each of the above populations.

Proposed dosing of Ferinject is via intravenous administration following calculation of total iron requirement. In heavy uterine bleeding, postpartum and IBD patients, the total iron dose (b) (4) maximum total dose not to exceed 2500 mg and maximum single dose not to exceed the lower of 15 mg/kg per dose or 1000 mg. Single doses would be administered every 7 days until the total prescribed dose has been administered. (b) (4)

(b) (4) In hemodialysis patients the prescribed iron requirement would be administered undiluted by rapid IV push injection as single 200 mg doses directly into the venous line of the dialyzer 2 to 3 times weekly until the total prescribed dose is given.

Background:
Iron deficiency is the most common cause of anemia worldwide. The majority of the total body iron is localized in hemoglobin in red blood cells. Because the body has a tightly regulated mechanism of absorption of dietary iron and no mechanism for excreting iron, iron deficiency anemia is most often due to blood loss or chronic dietary insufficiency. Iron deficiency anemia occurs in hemodialysis patients due to destruction of red blood cells during dialysis, along with anemia secondary to renal disease. Iron deficiency anemia can occur in women who routinely experience heavy menstrual periods and among women during the immediate post-partum period. The sponsor cites that as many as 37% of U.S. women in their third trimester of pregnancy suffer from iron deficiency anemia and 5% of births are complicated by severe postpartum anemia (hemoglobin <7 g/dL). The sponsor states that menorrhagia (heavy uterine bleeding) affects at least 10% of U.S. women and defines this as loss of >80 mL of blood per period. Inflammatory bowel disease can cause impaired iron absorption as well as loss of blood in the stool due to inflammation.

The sponsor's drug development plan investigated the use of Ferinject in limited numbers of iron deficient patients in each of these populations. The total number of patients exposed to Ferinject in the drug development program is 2049 patients. The sponsor requested priority review of the application but this was denied and the application is reviewed as a standard application.

Several iron products are currently available for treatment of iron deficiency anemia. These include oral iron as ferrous sulfate, which is most commonly used. Iron products approved for intravenous administration for treatment of iron deficiency anemia include: sodium ferric gluconate complex (Ferrlecit), iron sucrose (Venofer) and iron dextran (INFeD, Dexferrum, Proferdex). Maximum dose among these products in iron deficient hemodialysis patients is 100 mg of elemental iron over 2-5 minutes and in non-dialysis dependent chronic renal failure patients is 200 mg elemental iron over 2-5 minutes (Venofer). The Venofer labeling indicates there is limited experience with Venofer 500 mg given over 3.5-4 hours in non-dialysis dependent renal failure patients; but hypotension occurred in 2 of 30 patients treated. In peritoneal dialysis patients Venofer has been given as two 300 mg infusions over 1.5 hours separated by 2 weeks and followed after an additional 2 weeks by a 400 mg infusion given over 2.5 hours. Recommended dose of Ferrlecit is 125 mg elemental iron. Maximum recommended dose of iron dextran is 100 mg daily to total prescribed dose, with dose being given not faster than 50 mg iron/min. Because of concern for anaphylactic reactions, for iron dextran, administration of a test dose is recommended prior to administration of a therapeutic dose. There is no parenteral iron product specifically labeled for treatment of iron deficiency anemia in heavy uterine bleeding, post-partum or inflammatory bowel disease patients.

Findings of the Clinical Review:
A detailed clinical review of the application has been conducted by Dr. Min Lu (See Clinical Review, Min Lu, M.D., completed 5/31/07, signed 6/14/07).

Efficacy: The sponsor has investigated the use of Ferinject in iron deficiency anemia patients in a total of 7 randomized, controlled clinical studies in a variety of clinical populations. There were 2 studies [both were same design and were discontinued prematurely (sponsor states due to slow enrollment) and results combined for analysis] in women with heavy uterine bleeding, 3 studies in postpartum women within 6 days after delivery, 1 study in patients with inflammatory bowel disease, and 1 study in hemodialysis patients (1 study). [Note: For purposes of analysis and this review, the studies in heavy uterine bleeding are considered as one study]. Randomization was 1:1 in all studies except 1 post-partum anemia study and the inflammatory bowel disease study where randomization was 2:1 (Ferinject:oral iron). All 6 studies were open-label. Definition of iron deficiency anemia varied among the studies. Limits for hemoglobin (Hb), serum ferritin, and transferrin saturation (TSAT) for each controlled study are shown in the following table:

Criteria for Iron Deficiency Anemia in Controlled Clinical Studies

Study	Hb	Ferritin	TSAT
1VIT 4002/1VIT 4003[@]	≤11.4 g/dL and 2 mean Hb ≤11.0 g/dL	≤100 ng/mL	≤25%
1 VIT 03001	≤10.0 g/dL	≤500 ng/mL	≤50%
VIT-IV-CL-009	≤10.5 g/dL	NS	NS
1VIT06011	≤10.0 g/dL	≤100 ng/mL	≤25%
VIT-IV-CL-008	≤11.0 g/dL	<100 ng/mL	<20%
VIT-IV-CL-015	≤11.5 g/dL	<200 ng/mL	<20%

[@] two studies with similar design; both discontinued prematurely due to slow enrollment when approximately 61% of patients had been enrolled;

This reviewer's table, based on Dr. M. Lu's Clinical Review

In all studies treatment groups were reasonably well-balanced with regard to baseline demographics and anemia characteristics. In the studies which enrolled U.S. subjects, patients in the heavy uterine bleeding study were predominantly Black (50%) and Hispanic (27%), patients in post-partum anemia study 1VIT03001 were approximately 47% Caucasian, 30% Hispanic and 21% Black, and patients in post-partum anemia study 1VIT06001 were approximately 70% Caucasian, 13% Hispanic and 17% Black. In the other three studies the patients were virtually all Caucasian. Mean age was 39 years for the heavy uterine bleeding patients, 27 years for the post-partum anemia patients, 44 years for the inflammatory bowel disease patients, and 52 years for the hemodialysis patients. More than 75% of patients in both treatment groups completed the study in all these trials. Duration of treatment for efficacy assessment was 6 weeks in the heavy uterine bleeding and in 2 post-partum anemia studies, 12 weeks in the inflammatory bowel disease study and in 1 post-partum anemia study and 4 weeks in the hemodialysis study.

Results of the primary efficacy analysis for the controlled clinical studies are summarized in the following table:

Efficacy of Ferinject in Iron Deficiency Anemia in Various Populations (MITT[1] Population)

Population/ Study	Endpoint	Efficacy Endpoint Value		Statistical comparison
		Ferinject	Oral Iron[+]	
Heavy uterine bleeding/ 1VIT 4002/1VIT 4003*[@]	Patients with Hb increase ≥2 g/dL anytime during study (up to Day 42)	187/228 (82.0%)	139/225 (61.8%)	P<0.001
Post-partum anemia/ 1 VIT 03001	Patients with Hb increase ≥2 g/dL anytime during study (up to day 42)	162/168 (96.4%)	159/169 (94.1%)	Within sponsor's Non-inferiority margin of 15%[A]
VIT-IV-CL-009	Change in mean Hb at Week 12	3.34	3.18	Within sponsor's non-inferiority margin
1VIT06011*	Patients with Hb >12.0 g.dL prior to week 6	127/139 (91.4%)	98/147 (66.7%)	<0.001
Inflammatory bowel disease/ VIT-IV-CL-008	Change in mean Hb level at Week 12	3.60	3.29	Within sponsor's Non-inferiority margin of -.05 g/dL[A]
			Venofer	
Hemodialysis/ VIT-IV-CL-015	Patients with Hb increase ≥1 g/dL at Week 4	52/118 (44.1%)	41/116 (35.3%)	0.225 (formal statistical analysis not planned in the protocol)

[1] Modified intent-to-treat population: received at least 1 dose of study drug and had at least 1 post-baseline efficacy evaluation and (for post-partum anemia studies) had baseline hemoglobin <11.0 g/dL by 2 baseline measurements.

[+] oral iron dose -- ferrous sulfate 325 mg tablets (65 mg elemental iron) three times daily or 100 mg capsules twice daily

[*] superiority design (all other studies were non-inferiority design);

[@] two studies with similar design; both discontinued prematurely due to slow enrollment when approximately 61% of patients had been enrolled;

[A] lower bound of 95% confidence interval

This reviewer's table, based on sponsor's tables in Dr. M. Lu's Clinical Review, and tables in Dr. S. Misra's Statistical Review.

All controlled studies were open label with intravenously administered Ferinject being compared to orally administered ferrous sulfate except for the study in hemodialysis patients where the comparator was Venofer (iron sucrose). Each of the non-inferiority studies had substantial deficiencies with regard to justification of the non-inferiority margin used. These deficiencies are described in the Clinical Review (table on page 24 of review by Dr. M. Lu, completed 5/31/07 and in the Statistical Review by S. C. Misra, Ph.D., 6/26/07). Deficiencies included inconsistencies in cited populations, drug dosing, and efficacy endpoints between the

Ferinject studies and the cited publications and also the study margins for efficacy appeared too generous.

Generally, compliance in patients receiving Ferinject was somewhat higher than in patients receiving oral iron (e.g., in Study 1VIT4002/1VIT4003 approximately 98% of patients receiving Ferinject were ≥67% compliant as compared to 90% of patients receiving oral iron). Compliance with oral iron in these studies was described as at least two-thirds of prescribed study medication taken as reported by patients. Though Ferinject appeared to show greater efficacy than oral iron in the two superiority design studies (1VIT4002/1VIT4003 and 1VIT06011), success rates exceeded 60% in the oral iron group in each study. Formal statistical analysis was not planned for the hemodialysis study (VIT-IV-CL-015).

Safety: The submitted safety database for Ferinject included 2049 patients who have received Ferinject, 1237 with multiple doses in controlled clinical trials [including 2 open-label ongoing] (230, heavy uterine bleeding; 543, post-partum anemia; 183, inflammatory bowel disease; 281, hemodialysis). An additional 614 patients received single doses of Ferrinject in other studies.

In the controlled trials a total of 1527 patients have received control drug (577, placebo; 832, Venofer; 118, Venofer) and 2049 have received Ferinject. In these trials among the total 2049 patients who have received Ferinject, 10 patients (0.49%) have died and no patients who received control agent have died (Clinical Review, Dr. M. Lu). In the controlled, active comparator clinical efficacy trials there were 3 deaths---1 in post-partum anemia study 1VIT03001 eight days after receiving Ferinject, 1 in the inflammatory bowel disease trial 1 day after receiving Ferinject and 1 in the hemodialysis trial 9 days after receiving Ferinject. In the safety database there were 7 additional deaths of patients who had received Ferinject, including 2 in an uncontrolled hemodialysis study, 1 in a single-dose, cross-over (placebo) safety study in patients with iron deficiency anemia, and 2 in an ongoing, oral iron controlled trial in non-hemodialysis patients with chronic renal failure and 2 in an extension study in non-hemodialysis patients with chronic renal failure. Death was attributed to a likely cardiovascular cause in 5 of the 10 cases.

The distribution of these 10 deaths among the studies and a brief description of each case are provided in the following table. Each of the cases is described in detail in Dr. Lu's Clinical Review.

Summary of Deaths in Controlled Clinical Trials of Ferinject

Population	Deaths	Study	Description of deaths
Post-partum anemia	1	1 VIT 03001	27 yo African woman at U.S. site with Hgb 7.9 g/dL, TSAT 5%, previous history of anemia requiring transfusion during previous pregnancy; received Ferinject 1000 mg; was found 8 days later unresponsive at home with "frothy edema fluid" from her mouth.; resuscitation unsuccessful; autopsy showed dilated left ventricle, moderate bilateral pleural effusions, pulmonary edema and soft tissue edema. Cause of death listed as peripartal cardiomyopathy.
Inflammatory bowel disease	1	VIT-IV-CL-008	56 yo man (Bulgaria) with hx aortic valve stenosis, mitral insufficiency, ulcerative colitis and anemia. Had been hosp year prior to study with exertional dyspnea, anemia and ECG with positive myocardial ischemia, received RBC and Venofer infusions. Study screening Hb 5.5 g/dL, TSAT 2%, ferritin 14 ng/mL; received one dose Ferinject 1000 mg; one day later he suffered cardiac arrest at work and died. No autopsy.
Hemodialysis	1	VIT-IV-CL-015	57 yo man (Bulgaria) with diabetes mellitus, hypertension, chronic renal failure, received Ferinject dose, experienced clotting dialysis lines and filter later that day which resolved. Four days later admitted to ICU with large acute ST-elevation, anterior; developed congestive heart failure and died 4 days later.
Hemodialysis	2	VIT-53214	59 yo white woman with chronic renal failure, hx hypertension, tuberculosis, chronic persistent hepatitis B; received total of 1200mg Ferinject in 6 doses over 12 days; had abnormal chest x-ray 2 days before last dose. Two days after last dose patient was hospitalized with cough, weakness, dyspnea on exercise. Admitted for TB rx based on X-ray. Three weeks later "developed acute cardiac insufficiency" and died. No autopsy.
			54 yo woman (Romania) with chronic renal failure, hypertension, congestive heart failure, uremic cardiomyopathy; received total of 1600 mg Ferinject in 200 mg doses over 17 days; died suddenly at home 19 days after last dose. Cause of death listed by family doctor as heart failure.
Anemia	1	1VIT05006 (single dose safety cross-over study)	48 yo woman with hx anemia, gastric bypass for morbid obesity, depression, recurrent UTI, and hysterectomy; enrolled with Hb 11.4 g/dL, TSAT 4%, ferritin 5ng/mL; received placebo without problem; 8 days later received 1000 mg Ferinject; within next 2 weeks she was seen twice by physician and treated for earache (Cortisporn OTIC and hydrocordone) and later for URI symptoms (afebrile) diagnosed with URI and UTI and given Augmentin 10 day course; 2 days later she was transported to ER with shortness of breath, coughing, weakness, fatigue where she presented with severe respiratory distress and O_2 saturation 60%; chest X-ray showed extensive right lung infiltrate; she was intubated but became bradycardic and hypotensive, sufferend cardiac arrest and died; sputum and blood culture positive for aeromonas hydrophila; cardiac enzymes negative on ER admission. No autopsy.

Non-dialysis dependent chronic kidney disease	4	1VIT04004	85 yo man with hx of chronic kidney disease, atrial fibrillation, coronary artery disease with MI, prostate cancer, and pneumonia received 1000mg Ferinject (HB 10.2 g/dL). One month later had weakness, difficulty urinating, bladder outlet syndrome with bilateral hydronephrosis; urine and blood grew methicillin resistant staphylococcus; patient declined dialysis and medication to support blood pressure and died in hospice 2 days later.
		1VIT04004	76 yo man with hx of chronic kidney disease, ruptured abdominal aortic aneurysm; hypertension, peptic ulcer disease; received total 2000mg Ferinject as 3 doses over 30 days; 2 weeks after last dose was injured in auto accident and died next day.
		1VIT05005 (extension study)	86 yo man with hx chronic kidney disease, coronary artery disease, hypertension, type ii diabetes mellitus, and arthritis; received oral iron in sStudy 1VIT04004 then continued onto extension study; received 1000 mg Ferinject and 3 months later a second dose of 500 mg; 3 months later presented with bowel perforation with peritoneal abscesses diagnosed as acute diverticulitis with two ruptured diverticular perforations. Patient died 2 days later.
		1VIT04004 and 1VIT05005 (extension study)	64 yo woman with hx chronic kidney disease, type 2 diabetes mellitus, hypertension, and hyperlipidemia; received 1000mg Ferinject in 1VIT04004 study; 8 wks later continuted into 1VIT05005 extension study and received 500 mg Ferinject followed by another 500mg 4 days later and another 500 mg about 18 weeks later. Four wks later had exploratory laparotomy for biopsy of lymph nodes seen on CT; pathology showed granulomatous lymphadenitis.; during recovery from surgery patient developed massive GI bleeding and suffered cardiac arrest and died despite resuscitative efforts. No autopsy.

Reviewer's table, based on Clinical Review by Dr. M. Lu

In all completed studies serious adverse events were experienced by 3.2% of patients who received Ferinject, 1.2% of patients who received oral iron and 6.8% of patients who received Venofer; however, there was no remarkable pattern of differences among the adverse reactions reported for the three treatments. Numbers of particular events were small. Serious cardiac disorders were reported for 0.5%, 0.2% and 0.8% of patients who received Ferinject, oral iron and Venofer, respectively. Two patients who received Ferinject (and no patients in the other two groups) experienced myocardial infarction. One patient experienced myocardial infarction 2 weeks after last Ferinject dose (total 1200 mg over 3 weeks) and recovered; the other received Ferinject in VIT-IV-CL-015, had an MI 4 days later and subsequently died. Cases of serious infections were reported only for the parenteral iron treatments (Ferinject and Venofer).

In the completed controlled, multiple dose studies, adverse events led to study discontinuation in 2.1% of the Ferinject treated patients, 3.1% of the oral iron treated patients, and 2.5% of the Venofer treated patients. In these cases discontinuation was most commonly due to gastrointestinal causes for oral iron treated patients, renal transplant for the Ferinject treated patients, and gastrointestinal causes for the Venofer treated patients. Numbers of such events were small, especially for the Venofer group.

Two incidents of hypersensitivity events were reported in patients who received Ferinject, one mild in a patient on the same day after a first Ferinject dose and another which required treatment in a patient on the second day after a second Ferinject dose.

In the studies where the first Ferinject dose was high (1000 mg)(VIT-IV-008, VIT-IV-009, 1VIT03001, 1VIT04002/1VIT04003) clinical chemistry laboratory studies were remarkable for statistically significant (mostly not clinically significant) greater increases in GGT, ALT, bilirubin and decrease in potassium in Ferinject group as compared to oral iron.

A notable finding in the clinical laboratory evaluations was that in the studies where serum phosphate was measured (1VIT03001 [post-partum], 1VIT05006 [cross-over safety study], 1VIT04002/1VIT04003 [heavy uterine bleeding]), there were statistically significant decreases in the serum phosphate in the Ferinject treated patients as compared to the oral iron treated patients. The incidence of potentially clinically significant abnormal serum phosphate in the Ferinject group in these studies was 8.0% in 1VIT03001, 70.1% in 1VIT04002/1VIT04003 and 16.0% in 1VIT05006. Patients who received the oral iron control in 1VIT03001 and 1VIT04002/1VIT04003 had no clinically significant abnormal serum phosphate values and 9.9% of the patients following placebo control (cross-over study) had clinically significant abnormal serum phosphate values. There was no clear relationship between serum phosphate nadir and reported adverse events among patients in these studies, though there was a trend to more total adverse events in patients with lowest nadir.

Notable for the conduct of the studies is that though the protocols indicated that patients in whom the serum ferritin increased to above 800 ug/L and TSAT was greater than 50% were to have study drug discontinued, in fact, for Study VIT-CL-IV-009 (post partum patients) 53 (44%) patients who had serum ferritins above 800 ug/L at Week 1 or Week 2 and 1 who had a serum ferritin level of 1732 ug/L at Week 4 were not discontinued from study treatment (See Clinical Review, Dr. M. Lu). Similarly in Study VIT-CL-IV-015 (hemodialysis patients) a number of patients in the Ferinject group and in the Venofer group had study drug continued in spite of exceeding maximum ferritin levels stipulated by the stopping rules.

One patient who inadvertently received an overdose of Ferinject (1300 mg instead of calculated 800 mg) developed asymptomatic elevated LFTs after 12 weeks which persisted for 3 months but had returned to normal by 6 months later.

In the completed studies fewer than 10% of patients were age ≥65 years. No pregnant women or pediatric patients were studied.

Other Information:
Comments from Dr. Julie Vose, Chief, Hematology/Oncology, University of Nebraska Medical Center, Omaha, Nebraska: Dr. Vose was consulted as a Special Government Employee (SGE) for comment on this application. Dr. Vose was provided with summary information on the Ferinject application including Ferinject clinical development and parenteral iron product background and a description of agency safety concerns, including mortality, hypophosphatemia, descriptions of 7 deaths (up to time of consultation). Dr. Vose stated that the available data were not sufficient for her to conclude that the product is safe in that she could not explain the deaths of 3 patients (2 in hemodialysis patients) in the summary sent to her. She also was concerned that "limited dose ranging information may underscore the importance of the mortality findings." Dr. Vose acknowledged that a product that could safely and quickly deliver a "full" iron dose would be beneficial and would likely be used widely (depending on expense). (See Record of 1/22/07 Teleconference, signed in DFS 1/23/07, Dr. R. Rieves).

Statistics: The Statistical Review (S. C. Misra, Ph.D., 6/26/07) identified problems with justification of the use of open label non-inferiority design to establish efficacy compared to oral iron due to difference in route of administration and associated safety concerns, with justification of the non-inferiority margins (including lack of sufficient historical data, differences in treatment duration and study endpoints), and use of a post-hoc non-inferiority margin in one study. Regarding safety the Statistical Review states, "The results of these clinical trials show that the drug has an unfavorable risk profile due to a higher mortality associated with Ferinject as compared to available treatment (0.49% vs. 0.0%, 95% Confidence Interval (0.24%, 0.9%), nominal p-value=0.0067). A higher risk of at least one serious adverse event was associated with Ferinject use as compared to oral iron treatment (3.2% vs. 1.2%)."

The review concluded that in light of the safety findings the review team's expectation of superior efficacy of Ferinject compared to oral iron was met in one trial in patients with heavy uterine bleeding and in one trial in post-partum anemia patients which were designed as superiority trials but not in the other 3 trials where an non-inferiority design was used.

Chemistry, Manufacturing and Controls (CMC): CMC review (L. Epps, Ph.D./R Harapanhalli, Ph.D., 6/15/07) recommended that from a CMC standpoint the application is approvable, pending carton and labeling revisions. The review indicated the sponsor will be asked to submit updated stability results.

Product Quality Microbiology Review: The Microbiology review (S.E. Langille, Ph.D., 5/7/07) found that "the drug is (b) (4) and no deficiencies were identified. With regard to microbiological product quality the application was recommended for approval.

Pre-Clinical Pharmacology/Toxicology: The pharmacology/toxicology review (Y. Chopra, Ph.D., 6/5/07) found that the accumulation of the administered iron was 76% in red blood cells, 11% in liver, 2% in spleen and 1% in kidney. Repeat dose toxicity studies in rats and

dogs showed iron deposition in liver, spleen, lymph nodes and kidneys. Single intravenous doses of 0.24 g/kg in dogs and 1 g/kg in rats were not lethal. The animal toxicity studies did not identify any treatment-related changes in vital signs or any signs of cardiovascular effects in rats and mice. In the 26-week chronic IV injection toxicity study in dogs at week 13 showed a dose-related decrease in heart rate and slight effect on QT interval in male animals but were normal at 26 weeks. There was some increase in blood pressure at 2 hours post-dose. The drug was not genotoxic or mutagenic and exerted no adverse effects on fertility and reproductive parameters. Fetal malformations of cranial deformity with hydrocephaly in rabbits were found at a maternal toxic dose. Recommendation is made for designation of Pregnancy Category (b) (4)

Clinical Pharmacology and Biopharmaceutics: The clinical pharmacology review (C. S. John, Ph.D., 5/30/07) concluded that from the Clinical Pharmacology perspective the application was acceptable but found that "the relationship between dose and various pharmacodynamic variables indicate that Ferinject dose has not been optimized." The review commented, "Based upon the pharmacodynamic variables, such as, unsaturated iron binding capacity and mean changes in transferrin saturation from baseline at 24-36 hours data, it appears that a lower dose such as 500 mg and 800 mg may be equally efficacious clinically." It was recommended that the sponsor conduct a pharmacokinetic/pharmacodynamic study to explore the effectiveness and safety of lower Ferinject doses.

Discussion:
Though the clinical trials submitted had important design and analysis deficiencies, including that all were open-label, non-inferiority margins were not well-supported and per protocol analyses which excluded about 20% of patients in 3 of 6 studies were used as the primary efficacy population, because Ferinject is a chemical compound that can provide physiologically available iron, it is reasonable to conclude that Ferinject has some efficacy with regard to repletion of iron and treatment of anemia in iron deficiency anemia. However, the efficacy apparent in the submitted trials does not appear as particularly impressive, considering that the comparator in all but one study was oral iron, which is not 100% absorbed and for which adequate compliance in the studies was defined as at least two-thirds of prescribed doses taken.

Though the trials were not designed to test for a mortality effect of Ferinject and the studies involved different underlying disease populations, the collective safety information suggests that Ferinject may predispose patients to adverse cardiovascular events which may lead to death. There was a statistically significant greater mortality in the Ferinject treated patients (0.49%) as compared to the comparator (oral iron or Venofer)-treated patients (0.0%) in the controlled clinical trials. The available data are not sufficient to clarify any possible relationship between dose and/or dosage regimen and this apparent risk. The risk of exploring this possible association between Ferinject and cardiovascular adverse events in order to allow continued pursuit of marketing approval for Ferinject should be weighed against the value of having a new injectable iron product to add to the existing armamentarium of several such products.

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kathy Robie-Suh
6/29/2007 07:59:35 PM
MEDICAL OFFICER